UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

05 JUN 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review on Glyphosate

FROM: Esther Rinde, Ph.D. E.R.
Manager, Carcinogenicity Peer Review
Health Effects Division (H7509c)

TO: Addressees

Attached for your review is a package on Glyphosate prepared by William Dykstra, Ph.D.

A meeting to consider the classification of Glyphosate is scheduled for Wednesday June 19, 1991, at 10:00 am in Room 821, CM2.

Addressees

P. Fenner-Crisp
W. Burnam
R. Engler
R. Hill
R. Beliles
K. Baetcke
J. Quest
M. Van Gemert
M. Copley
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MEMORANDUM

SUBJECT: Peer Review of Glyphosate

40 CFR 180.364
TOX Chem. No.: 661A

FROM: William Dykstra, Ph.D. William Dykstra 5/23/91
Review Section I
Toxicology Branch I
Health Effects Division (H7509C)

TO: Esther Rinde, Ph.D.
Manager, Peer Review for Oncogenicity
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

THRU: Roger L. Gardner, Section Head
Review Section I Roger L. Gardner 5-24-91
Toxicology Branch I
Health Effects Division (H7509C) 6/3/91

C. Background Information

Glyphosate is the isopropylamine (IPA) or sodium salt of N-(phosphonomethyl) glycine. It is sold under the trade names of Roundup, Rodeo, Shackle, and Polado. Glyphosate is a plant growth regulator herbicide which is used to control grasses, sedges, and broadleaf weeds. Its mode of activity is the inhibition of amino acid synthesis.

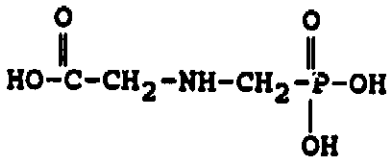
Tolerances established for glyphosate and its aminomethyl phosphonic acid (AMPA) metabolite in 40 CFR 180.364 include the following:

IPA salt of glyphosate: soybeans, cotton, corn, sorghum, wheat, rice, vegetables, citrus fruits, pome fruits, stone fruits, tropical fruits, pastures, and alfalfa.

Sodium salt of glyphosate: sugarcane.

DISCARD 6/3/91

Structure



Glyphosate

On February 11, 1985, the carcinogenic potential of glyphosate was first considered by a panel comprised of members of the Toxicology Branch of the Hazard Evaluation Division. That committee, in a consensus review dated March 4, 1985, classified glyphosate as a group C carcinogen based on an increased incidence of renal tubular adenomas in male mice. According to the consensus review, the tumor is rare, it occurred in a dose-related manner, and the incidence was outside the reported historical control range. The committee also concluded that dose levels tested in a 26-month feeding study were not adequate for the assessment of glyphosate's carcinogenic potential in rats.

The kidney slides from the long-term mouse feeding study were subsequently reexamined, and one pathologist diagnosed an additional kidney tumor in control males. These equivocal findings were presented to the FIFRA Science Advisory Panel (SAP) which proposed that glyphosate be classified into Group D (inadequate animal evidence of carcinogenic potential). The SAP concluded that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the oncogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings.

D. Evaluation of Carcinogenicity Data

1. Reference Lankas, G. P. December 23, 1981. A Lifetime Study of Glyphosate in Rats. Unpublished report No. 77-2062 prepared by BioDynamics, Inc. EPA Acc. Nos. 247617 - 247621. MRID 00093879.

a. Experimental Design

The lifetime feeding study in Sprague-Dawley rats at 50/sex/dose was tested at dietary concentrations of glyphosate of 0, 30, 100, and 300 ppm. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in female rats were maintained. No effect of treatment on the incidence of nonneoplastic lesions was noted.

b. Discussion of Tumor Data

An increase in the incidence of interstitial cell tumors of the testes was observed in the rats. Because of the absence of a dose-dependent effect, the lack of preneoplastic changes, the wide variability in the spontaneous incidence of this tumor, the similarity in incidences between the high-dose group and the historical controls, and lack of any evidence of genotoxicity, it was concluded by the previous Peer Review Committee that the observed incidence did not demonstrate an oncogenic response.

Additionally, there was the question of possible thyroid carcinomas in high-dose females. After a review of the slides by a consulting pathologist, and a reassessment of all relevant data, including the fact that no effect of treatment on tumor latency or the combined incidences of adenoma and carcinoma was apparent, the earlier Peer Review Committee concluded that the data did not demonstrate a carcinogenic response in the thyroid.

c. Nonneoplastic lesions

The rat study was also reviewed for evidence that the highest dose tested (HDT) was a maximum tolerated dose (MTD). No effects of treatment on survival, body weight gain, clinical pathology, or findings at necropsy were noted. Therefore, there is no evidence that the highest dose tested was an MTD.

The new chronic toxicity/oncogenicity rat study now being presented to the Peer Review Committee is a replacement study for the 26-month 1981 chronic rat study.

2. Reference - L.D. Stout and F.A. Ruecker. Chronic Study of glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; September 26, 1990. MRID No. 416438-01; Historical Controls; MRID No. 417287-00.

a. Experimental Design

Randomized groups of 60 male and 60 female young (8 weeks) Sprague-Dawley rats were fed dietary levels of 0, 2000, 8000, and 20,000

ppm of technical glyphosate for 2 years. At 12 months, 10/sex/group were sacrificed.

Animals were observed twice daily for toxicity and mortality and were given weekly clinical examinations. Body weight and food consumption were determined each week for the first 13 weeks and monthly, thereafter. Ophthalmic examinations were performed at pretest and just prior to terminal sacrifice.

Urinalysis, hematology, and clinical chemistry determinations were conducted on 10 animals/sex/dose each at 6, 12, 18, and 24 months.

All animals were given a complete gross necropsy. Brain, kidneys, liver, and testes with epididymides were weighed. Approximately 40 tissues and all gross lesions were preserved and examined microscopically for each animal.

The NOEL for systemic effects was 8000 ppm. The LEL was 20,000 ppm (HDT) and the effects consisted of decreased body weight and body weight gain in females, cataracts in males, decreased urinary pH in males, increased relative liver weight (to body) at 12 months, and increased absolute and relative liver weight (to brain) at 24 months in males.

b. Discussion of Tumor Data

Age-adjusted, statistical analyses of the tumor data performed by the statisticians of SACB are presented. Also, the statistical analyses by the registrant are included.

i. Pancreas (Tables 1 - 3)

Low-dose and high-dose males had a statistically significant increased incidence of pancreatic islet cell adenomas.

Table 1: Glyphosate - Sprague-Dawley Male Rats, Pancreatic Islet Cell Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20,000
Carcinomas	1/43[a]	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
p =	0.159	0.409(n)	0.467(n)	0.472(n)
Adenomas	1/43	8/45	5/49	7/48[b]
(%)	(2)	(18)	(10)	(15)
p =	0.170	0.018*	0.135	0.042*
Adenomas/carcinomas	2/43	8/45	5/49	7/48
(%)	(5)	(18)	(10)	(15)
p =	0.241	0.052	0.275	0.108
Hyperplasia only	2/43	0/45	3/49	2/48[c]
(%)	(5)	(0)	(6)	(4)
p =	0.323	0.236(n)	0.526(n)	0.649(n)
Registrant's Analysis				
Carcinomas	1/58	0/57	0/60	0/59
(%)	(2)	(0)	(0)	(0)
Adenomas	1/58	8/57[d]	5/60	7/59
(%)	(2)	(14)	(8)	(12)
Adenomas/carcinomas	2/58	8/57	5/60	7/59
(%)	(3)	(14)	(8)	(12)
Hyperplasia only	2/58	0/57	4/60	2/59
(%)	(5)	(0)	(7)	(3)

+ Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacificed before week 55.

(n) Negative change from control.

[a] First carcinoma observed at week 105, dose 0 ppm.

[b] First adenoma observed at week 81, dose 20000 ppm.

[c] First hyperplasia observed at week 91, dose 20000 ppm.

[d] $p \leq 0.05$; Fisher's Exact test with Bonferoni correction.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If * then $p < 0.05$ and if * then $p < .01$.

Historical control data on the incidence of pancreatic islet cell tumors from Monsanto's EHL are shown in Table 2 below.

Table 2: EHL 87122 - Historical Control Information for Histopathological Findings (All Deaths)

Terminal Necropsy Study	Months of Date	Study Length (Months)	No. Observed	% Affected	% Affected
1	07/83	24	68	2	2.9
2	02/85	23	59	5	8.5
3	10/85	24	69	4	5.8
4	06/85	24	57	1	1.8
5	09/88	24	60	5	8.3
6	01/89	24	60	3	5.0
7	03/89	24	59	3	5.1

It can be seen from the study results that the incidences of the pancreatic islet cell adenomas at the low- and high-dose group exceed the historical control range of 1.8 to 8.5 percent. However, there is no dose-response relationship in the occurrence of these tumors in males, no progression to carcinoma, and the incidence of hyperplasia is not dose-related.

The incidences of islet cell pancreatic tumors the first rat study (Bio/dynamics Project No. 77-2062) are shown in Table 3. The incidence of pancreatic islet cell tumors for the two studies does not show a dose-related increase in adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%) (see below).

Table 3: Incidence of Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats Given Diets Containing Glyphosate for 26 Months (first rat feeding study).

Tumors	Dose (mg/kg/day) 0	3	10	30
Hyperplasia (%)	3/50 (6)	2/49 (4)	1/50 (2)	0/50 (0)
Adenomas (%)	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
Carcinomas (%)	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)
Adenoma/carcinoma (%)	0/50 (0)	5/49 (10)	2/50 (4)	3/50 (6)

Open literature information (data attached) provided by Monsanto from other laboratories shows a prevalence up to 17.0 percent in untreated Sprague-Dawley rats in recent studies.

Due to the high incidence of islet cell pancreatic adenomas in each male treated group, in comparison to concurrent controls, TB-I recommends that the HED Peer Review Committee review the oncogenic potential of glyphosate with respect to this tumor type.

ii. Thyroid (Tables 4 - 6)

C-cell adenomas were slightly increased in male and female mid- and high-dose groups as shown in Tables 4 and 5 below.

Since there was no dose-response in adenomas in either sex, no progression to carcinoma in a dose-related manner, no significant dose-related increase in severity of grade or incidence in hyperplasia, and in light of historical controls adenomas, the C-cell adenomas in males and females are not considered compound-related.

Historical control ranges for the thyroid tumors in Spargue-Dawley rats were reported as shown in Table 6.

Table 4: Glyphosate - Sprague-Dawley Male Rats, Thyroid C-Cell Tumor Rates+ and Cochran-Armitage Trend and Fisher's Exact Test Results (p values).

Tumors	Dose (ppm) 0	2000	8000	20,000
Carcinomas	0/54	2/55[a]	0/58	1/58
(%)	(0)	(4)	(0)	(2)
p =	0.452	0.252	1.000	0.518
Adenomas	2/54[b]	4/55	8/58	7/58
(%)	(4)	(7)	(14)	(12)
p =	0.069	0.348	0.060	0.099
Adenoma/carcinoma	2/54	6/55	8/58	8/58
(%)	(4)	(11)	(14)	(14)
p =	0.077	0.141	0.060	0.060
Hyperplasia only	4/54	1/55	5/58[c]	4/58
(%)	(7)	(2)	(9)	(7)
p =	0.312	0.176	0.546	0.601
Registrants Analysis				
Carcinoma	0/60	2/58	0/58	1/60
(%)	(0)	(3.4)	(0)	(1.7)
Adenomas	2/60	4/58	8/58	7/60
(%)	(3.3)	(6.9)	(13.8)	(11.7)
Hyperplasia	5/60	1/58	6/58	5/60
(%)	(8.3)	(1.7)	(10.3)	(8.3)

[a] First carcinoma observed at week 93 at 8000 ppm.

[b] First adenoma observed at week 54 at 0 ppm.

[c] First hyperplasia observed at week 54 at 8000 ppm.

+ Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacificed before week 55.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$ and if then $p < .01$.

Table 5: Glyphosate - Sprague-Dawley Female Rats, Thyroid C-Cell Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Tests Results (p values).

Tumors	Dose (ppm) 0	2000	8000	20,000
Carcinomas	0/57	0/60	1/59[a]	0/55
(%)	(0)	(0)	(2)	(0)
p =	0.445	1.000	0.509	1.000
Adenomas	2/57	2/60	6/59[b]	6/55
(%)	(4)	(3)	(10)	(11)
p =	0.031*	0.671(n)	0.147	0.124
Adenoma/carcinoma	2/57	2/60	7/59	6/55
(%)	(4)	(3)	(12)	(11)
p =	0.033*	0.671(n)	0.090	0.124
Hyperplasia only	10/57[c]	5/60	7/59	4/55
(%)	(18)	(8)	(12)	(7)
p =	0.113	0.112	0.274	0.086(n)
Registrants Analysis				
Carcinoma	0/60	0/60	1/60	0/60
(%)	(0)	(0)	(1.7)	(0)
Adenomas	2/60	2/60	6/60	6/60
(%)	(3.3)	(3.3)	(10)	(100)
Hyperplasia	10/60	5/60	9/60	5/60
(%)	(15.7)	(8.3)	(15)	(8.3)

[a] First carcinoma observed at week 93 at 8000 ppm.

[b] First adenoma observed at week 72 at 0 ppm.

[c] First hyperplasia observed at week 54 at 8000 ppm.

[+] Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacificed before week 55.

(n) Negative change from control.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If * then $p < 0.05$ and if then $p < .01$.

Table 6: Historical Control Data for the Incidence of Thyroid C-Cell Tumors in Sprague-Dawley Strain Rats.

Tumor	Range (%) Males	Females
Carcinomas	0 - 5.2	0 - 2.9
Adenomas	1.8 - 10.6	3.3 - 10
Hyperplasia	4.3 - 20	4.3 - 16.9

iii. Liver (Table 7)

There was a slight dose-related increase in hepatocellular adenomas in males but the incidence was within the range of historical controls from Monsanto's EHL. The reported historical control incidence of hepatocellular carcinomas ranged from 0 to 6.7%, and that for hepatocellular adenomas ranged from 1.4 to 18.3%. There were no dose-related increases in the incidences of other hepatocellular lesions.

Table 7: Glyphosate - Sprague-Dawley Male Rats, Hepatocellular Tumor Rates[+] and Cochran-Armitage Trend and Fisher's Exact Test Results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20,000
Carcinomas	3/44	2/45	1/49	2/48[a]
(%)	(7)	(4)	(2)	(4)
p =	0.324	0.489(n)	0.269(n)	0.458(n)
Adenomas	2/44	2/45	3/49	7/48[b]
(%)	(5)	(4)	(6)	(15)
p =	0.016*	0.683(n)	0.551	0.101
Adenoma/carcinoma	5/44	4/45	4/49	9/48
(%)	(11)	(9)	(8)	(19)
p =	0.073	0.486(n)	0.431(n)	0.245
Hyperplasia only	0/44	0/45	1/49[c]	0/48
(%)	(0)	(0)	(2)	(0)
p =	0.462	1.000	0.527	1.000
Registrants Analysis				
Carcinoma	3/60	2/60	1/60	2/60
(%)	(5)	(3.3)	(1.7)	(3.3)
Adenomas	2/60	2/60	3/60	7/60
(%)	(3.3)	(3.3)	(5)	(11.7)
Hyperplasia	0/60	0/60	1/60	1/60
(%)	(0)	(0)	(1.7)	(1.7)

[a] First carcinoma observed at week 85 at 20,000 ppm.

[b] First adenoma observed at week 88 at 20,000 ppm.

[c] First hyperplasia observed at week 89 at 8000 ppm.

[+] Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacificed before week 55.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If * then $p < 0.05$ and if * then $p < .01$.

As can be seen from the hepatocellular tumor data, the historical controls, and the nonneoplastic liver lesions data, there is no progression from adenoma to carcinoma and the nonneoplastic lesions (hyperplasia, centrilobular necrosis, and focus of cell alteration) do not show a compound-related effect. Therefore, the slightly increased occurrence of hepatocellular adenomas in males is not considered compound-related.

c. Nonneoplastic lesions

There were no compound-related nonneoplastic lesions.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The HDT was 20,000 ppm which is the limit dose for carcinogeni-city studies in rats.

3. Mouse Study - 24-Month Study (1983)

Reference BioDynamics Inc., July 21, 1983. An 18-Month Study of Glyphosate in the Mouse. Unpublished Report No. 77-2061. EPA Acc. Nos. 251007 - 251009, and 251014.

a. Experimental Design

The oncogenicity study in CD-1 mice at 50/sex/dose was tested at dosages of 1000, 5000, and 30,000 ppm.

b. Discussion of Tumor Data

Glyphosate produced an equivocal oncogenic response in the mouse, causing an incidence of renal tubular adenomas in males of 0, 0, 1, and 3 in the control, low-, mid-, and high-dose groups, respectively.

The Toxicology Branch Ad Hoc Oncogenicity Peer Review Committee tentatively classified glyphosate as a "Class C" carcinogen. The kidney slides were reexamined by a consulting pathologist, and data were submitted indicating that an additional kidney tumor had been found in control males.

The Agency then requested that additional kidney sections from the mouse study be prepared and examined. The resultant microslides were examined by a number of pathologists. These examinations revealed no additional tumors, but confirmed the presence of the tumors identified in the original study report. The tumor in the control kidney was not present in any of the additional sections.

Because of the equivocal nature of the findings, the Toxicology Branch Ad Hoc Oncogenicity Peer Review Committee asked the expert

assistance of the FIFRA Science Advisory Panel (SAP) in determining the proper Weight-of-the-Evidence classification of the study. After reviewing all the available evidence, the SAP proposed that glyphosate be classified as "Class D," or having "inadequate animal evidence of oncogenicity." The principal reason for this assessment by SAP was their determination that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the oncogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings.

HED has deferred a decision on the repeat of an additional mouse oncogenicity study until the 1990 rat feeding study has been evaluated by the Peer Review Committee.

Other nonneoplastic changes noted in high-dose male mice included centrilobular hypertrophy and necrosis of hepatocytes, chronic interstitial nephritis, and proximal tubule epithelial cell basophilia and hypertrophy in the kidneys of females. The no-observable-effect level (NOEL) for nonneoplastic chronic effects was the mid-dose level, 5000 ppm.

E. Additional Toxicology Data on Glyphosate

1. Metabolism of Glyphosate

Sprague-Dawley rats (3 to 6/sex/ group) were given a single oral or intravenous dose of C-14 glyphosate (radiochemical purity > 99%). Expired air, blood, urine, and feces were collected during a 7-day postdosing period for analysis of radiolabeled content by liquid scintillation counting (LSC). Urine and feces were also specifically analyzed for glyphosate and its metabolites using two different high pressure liquid chromatography techniques and LSC.

The results show that 30 to 36 percent of orally and intravenously administered glyphosate is absorbed.

Data showed that less than 0.27 percent of the dose was expired as CO_2 within 24 hours. Glyphosate, per se, was the highest radiolabeled material found in the urine and feces. The minimum level of glyphosate extracted from urine and feces was 97.5 percent. AMPA was found in the excreta of animals at levels of 0.2

to 0.3 percent and 0.2 to 0.4 percent in urine and feces, respectively. No detectable AMPA metabolite was found in intravenously dosed rats and high dose, orally dosed rats. There were no other metabolites of glyphosate formed.

Based on analysis of radioactivity in urine and feces and using the "sigma-minus" plotting method, males and females had alpha half-lives of 2.11 and 7.52 hours and 5.00 to 6.44 hours, respectively. The beta half-lives of males and females in these groups ranged from 69.0 to 181 hours for males and 79.9 to 337 hours for females.

Less than 1 percent of the absorbed dose remains in tissues and organs, primarily bone. Repeated dosing with glyphosate does not significantly change the metabolism, distribution, or excretion of glyphosate.

N-Nitrosoglyphosate (NNG)

The Agency has determined that oncogenicity testing of nitroso contaminants will normally be required only in those cases in which the level of nitroso compounds exceeds 1.0 ppm (see "Pesticide Contaminated with N-nitroso Compounds, proposed policy 45 FR 42854 (June 25, 1980)"). The levels of NNG in technical glyphosate have been examined by HED.

The overall NNG content in individual samples of technical glyphosate analyzed at production plants is shown below:

Analyzed Samples Containing NNG		NNG Observed
No. Samples	Per cent	(ppm)
2035	92.6	< 1000
124	5.6	1000 - 1500
24	1.1	1500 - 2000
13	0.6	2000 - 3000
2	0.1	> 3000

The overall data show that 92.6 percent of the individual glyphosate samples analyzed contain less than 1.0 ppm (1000 ppb) of NNG. TB concluded that the NNG content of glyphosate technical is not toxicologically significant.

2. Mutagenicity

Glyphosate has been tested in several mutagenicity assays and found to be negative in each of the three categories recommended for evaluating genotoxic potential. The acceptable studies include the following: Ames Assay, both with and without S-9, up to toxicity or 5000 ug/plate, in vivo cytogenetic assay in rat bone marrow up

to 1000 mg/kg, mammalian gene HGPRT mutation assay in CHO cells *in vitro* both with and without S-9 up to toxic levels (10 mg/mL) and Rec- assay with *B. subtilis* up to 2000 ug/disk.

Unacceptable studies which were also negative included DNA repair in rat hepatocytes between 1.35×10^{-5} and 1.25×10^{-1} mg/mL, and a dominant lethal assay in mice up to 2000 mg/kg.

3. Developmental Toxicity

A teratology study in rats tested levels of 0, 300, 1000, and 3500 mg/kg/day showed no evidence of malformations observed in the study. Evidence of developmental toxicity in the form of unossified sternebrae and decreased fetal body weight was noted in fetuses from the high dose (3500 mg/kg/day). This dose was also toxic to dams as evidenced by weight gain deficits, altered physical appearance, and mortality during treatment. The developmental and maternal toxic NOEL for this study was 1000 mg/kg/day.

A teratology study in rabbits tested at dosage levels of 0, 75, 175, or 350 mg/kg/day showed no evidence of malformations observed. The highest dose tested was toxic to does as evidenced by altered physical appearance and mortality. No treatment-related developmental effects were noted. The NOEL for maternal toxicity is 175 mg/kg/day and the NOEL for developmental toxicity is 350 mg/kg/day.

In the three-generation rat reproduction study and addendum, the only toxicologically significant finding was focal renal tubular dilation in the kidneys of male pups from the F_{3b} generation of high-dose dams (30 mg/kg/day). The NOEL for this effect was 10 mg/kg/day. No effects on fertility, reproductive, or other study parameters were noted.

4. Structure - Activity Relationships

There currently are no structurally related pesticides registered by the Agency which resemble glyphosate. A nonregistered pesticide, sulfosate, has been reviewed for carcinogenic potential in mice and rats, but has not received secondary review. Sulfosate was negative for carcinogenic potential.

5. Acute, Subchronic and Chronic Feeding/ Oncogenicity Data

Glyphosate has a rat oral LD_{50} of 4320 mg/kg (both sexes), and a dermal LD_{50} greater than 7940 mg/kg in rabbits. New subchronic studies are not required since adequate chronic studies are available. Older subchronic studies were performed by IBT.

A 1-year chronic feeding study in dogs at 6/sex/dose was tested doses of 0, 20, 100, and 500 mg/kg/day, administered by capsule. The NOEL for the study was 500 mg/kg/day (HDT).

F. Weight of Evidence Considerations

The Committee should consider the following facts regarding the toxicology data on glyphosate in a weight-of-the-evidence determination of carcinogenic potential.

1. Glyphosate was associated with increased incidences of pancreatic islet cell tumors in male Sprague-Dawley rats at all treatment levels in comparison to the concurrent control group. The low- (14%) and high-dose group (12%) incidences exceeded the 0 to 8.5% range of historical controls from Monsanto's EHL data base. However, the occurrence of the pancreatic islet cell tumors in males was not dose-related.

   No increased incidence of these tumors was observed in female rats in comparision to concurrent controls.

2. There was no evidence of genotoxicity for glyphosate.

3. The open literature cited by the registrant shows a range of 0 to 17% for pancreatic islet cell tumors in Sprague-Dawley male rats which surpasses the incidence of 14% and 12% at the high and low doses, respectively, in the 2-year carcnogenicity study.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate; 2-Year Combined Chronic Toxicity/ Carcinogenicity Study in Sprague-Dawley Rats - List A Pesticide for Reregistration

Caswell No.: 661A
Project No.: 0-2037
Case No.: 103601
Submission No.: S384281
MRID No.: 416438-01
(Volume 1-6)

FROM: William Dykstra, Ph.D. William Dykstra 5/14/91
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Lois Rossi, PM 74
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Special Review and Reregistration Division (H7508C)

and

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THRU: fn Roger Gardner, Section Head Roger M. Hurley 5/14/91
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

Requested Action

Review new 2-year chronic toxicity/carcinogenicity study in rats with glyphosate.

Conclusion and Recommendation

1. Due to the high incidences of pancreatic islet cell tumors in each of the treated male groups (2000, 8000, and 20,000 ppm in comparison to concurrent controls, Toxicology Branch I has recommended that the carcinogenic potential of glyphosate be addressed by the Peer Review Committee. The approximate date on which this issue will be considered is mid-June 1991.

2. The study is acceptable as core-guideline data. A Data Evaluation Report of the study is attached.

The NOEL is the mid-dose of 8000 ppm and the LEL is the high-dose of 20,000 ppm. At the LEL, the effects were decreased body weight and body weight gain in females, cataracts in males, decreased urinary pH in males, increased relative liver weight (to body) at 12 months, and increased absolute and relative liver weight (to brain) at 24 months in males.

Attachment

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Reviewed By: William Dykstra, Ph.D. William Dykstra 5/14/91
Section I, Toxicology Branch I - IRS (H7509C)
for Secondary Reviewer: Roger Gardner, Section Head Pamela M. Hurley 5/14/91
Section I, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: 83-5 - Combined Chronic Toxicity/Carcinogenicity - Rats

TOX Chem No.: 661A

Accession No.: N/A

MRID No.: 416438-01 (Volumes 1-6)

Test Material: Glyphosate, technical; 96.5% purity; Lot XLH-264

Synonym: Roundup

Study No.: MSL-10495

Sponsor: Monsanto Company
St. Louis, MO

Testing Facility: Monsanto Environmental Health Laboratory
St. Louis, MO

Title of Report: Chronic Study of Glyphosate Administered in Feed to Albino Rats.

Authors: L.D. Stout and F.A. Ruecker

Report Issued: September 26, 1990

Conclusions: Glyphosate was fed to randomized groups of 60/sex/dose Sprague-Dawley rats at doses of 0, 2000, 8000 and 20,000 ppm.

The NOEL for systemic effects is 8000 ppm (the mid-dose). At 20,000 ppm (LEL, HDT), the effects were decreased body weight and body weight gain in females, cataracts in males, decreased urinary pH in males, increased relative liver weight (to body) at 12 months, and increased absolute and relative liver weight (to brain) at 24 months in males.

Due to the high incidence of pancreatic islet cell adenomas in each of the treated male groups in comparison to concurrent controls, Toxicology Branch I (TB-I) has recommended that the carcinogenic potential of glyphosate be addressed by the Peer Review Committee.

Classification: Core-Guideline

Special Review Criteria (40 CFR 154.7): N/A

A. Materials:

1. Test Compound - Glyphosate technical; Description: White powder; Batch No.: XLH-264; Purity: 96.5 percent; Contaminants: List in CBI appendix.

2. Test Animals - Species: Albino rat; Strain: Sprague-Dawley; Age: 8 weeks; Weight: Males 284 g, Females 221 g; Source: Charles River Breeding Laboratory, Portage, MI

B. Study Design:

1. Animal Assignment - Animals were assigned randomly to the following test groups:

Test Group	Dose in Diet (ppm)	Main Study 24 Months Male	Main Study 24 Months Female	Interim Sac. 12 Months Male	Interim Sac. 12 Months Female	Total Number of Animals Male	Total Number of Animals Female
Control	0	50	50	10	10	60	60
Low (LDT)	2000	50	50	10	10	60	60
Mid (MDT)	8000	50	50	10	10	60	60
High (HDT)	20,000	50	50	10	10	60	60

2. Diet Preparation - Diet was prepared weekly and stored at room temperature. Samples of treated food were analyzed for stability and concentration routinely.

Results - With respect to stability, diets sampled at the low and high concentrations after 7 and 14 days of open container storage at room temperature averaged 94 percent of day 0. Diet analyses for concentration showed all reported values, except one, to be within 20 percent of nominal levels. Homogeneity analyses of the 2000 and 20,000 ppm diets showed the coefficient of variation to be less than 5%. The following results, summarized in the report, are of dietary concentrations during the study.

	Test Groups T-1	T-2	T-3
Target Exposure (ppm)	2000	8000	20,000
Study Mean Concen. (ppm)	1900	7600	19,000
Standard Deviation (ppm)	140	440	1030
Study Average (% Target)	95	95	95

3. Animals received food (Purina Rodent Chow #5002) and water ad libitum.

4. Statistics - The following statistical procedures were used to detect statistically significant differences between treated animals and their respective controls.

a. Dunnett's Multiple Comparison Test (two-tailed) - In-life body weights, cumulative body weight changes, food consumption, absolute leukocyte counts, reticulocyte counts, urine pH, urine specific gravity, and clinical chemistry data obtained at months 6, 12, and 18 using the KDA clinical analyzer.

b. Fisher's Exact Test (one-tailed) - Incidence of selected ocular lesions.

c. Fisher's Exact Test (one-tailed) with Bonferroni Inequality Procedure (to adjust for false positives resulting from multiple comparisons) - The incidences of nonneoplastic microscopic lesions were tested at the $p \leq 0.01$ level. The incidences of neoplastic microscopic lesions were tested at $p \leq 0.05$ and ≤ 0.01 levels.

d. Mortality Data - Analyzed by SAS (Statistical Analysis System, SAS Institute, Cary, North Carolina) lifetable procedure which includes determination of the Generalized Wilcoxin and Generalized Savage statistics.

e. Peto Analysis - Inspection of the histopathologic data was used to select lesions for statistical analysis by the prevalence methods of Peto, et al. 1980.

5. Quality assurance was performed and signed by Arthur Uelner on September 12, 1990.

C. Methods and Results:

1. Observations - Animals were inspected twice daily for signs of toxicity and mortality and clinical examinations were performed once weekly.

Results

There were no compound-related toxic or clinical signs during the study. The incidences and types of observations were noted with similar occurrence and frequency between control and treated rats of both sexes.

Mortality (Survival) - There was no compound-related effect on survival. As presented in the report, survival was comparable between control and treated rats of both sexes.

Group/ Period	6 Months	12 Months	18 Months	Term
	Percent Survival			
MN	98	90	73	29
M1	98	90	76	38
M2	100	98	84	34
M3	100	96	84	34
FN	100	94	76	44
F1	100	100	80	44
F2	100	98	70	34
F3	96	90	76	36

2. Body Weight - They were weighed once weekly for 13 weeks, then monthly for remainder of study.

Results - There were no statistically significant decreases in body weight or body weight gain in males during the study. In high-dose females, body weight decreases were statistically significant starting on day 51 throughout month 20. The mean body weight of high-dose females was decreased by 3 percent at day 51, 14 percent at month 20, and 3 percent of control at month 24. By month 20, body weight gain was decreased by 23 percent in high-dose females in comparison to controls. Therefore, the NOEL for decreased body weight and body weight gain is the mid-dose of 8000 ppm. Body weights of the groups of female rats are shown below.

Females: Mean Body Weight (Grams)

Study Week	1	7	13	81	104
Dose (ppm)					
0	220.9	296.8	326.0	543.2	488.2
2000	220.7	220.9	327.9	523.4	535.6
8000	220.8	299.4	329.1	540.0	542.6
20,000	220.8	287.7*	314.0*	470.6**	471.4
% B.W. Gain (High-Dose Animals)	0	-11.9%	-11.4%	-22.7%	-6.4%

*p < 0.5, **p < 0.01

3. Food Consumption and Compound Intake - Consumption was determined and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.

Results

Food Consumption - There were no statistically significant decreases in food consumption in either treated sex in comparison to controls during the study.

Study averages for consumption of test material (mg glyphosate/kilogram body weight/day), based on the target concentrations, were approximately 89, 362, and 940 in males and 113, 457, and 1183 in females for the low-, mid-, and high-dose groups, respectively.

4. Ophthalmalogical examinations were performed at pretest and twice prior to terminal sacrifice on all animals by Dr. Cecil Moore and Dr. Lionel Rubin.

Results - Both Dr. Moore and Dr. Rubin found statistically significant increases in cataracts and lens abnormalities in high-dose male rats in comparison to controls at terminal sacrifice. The results are shown below as presented in the report.

	MOORE			RUBIN		
Group	Animals Examined	Animals With Lens Abnormalities[a]	% Animals With Lens Abnormalities[a]	Animals Examined	Animals With Lens Abnormalities[b]	% Animals With Lens Abnormalities[b]
MN	15	0	0	14	1	7
M1	22	1	5	22	2	9
M2	18	3	17	17	3	18
M3	20	5*	25	19	8*	42
FN	23	0	0	23	1	4
F1	24	0	0	24	1	4
F2	17	1	6	17	1	6
F3	19	2	11	19	3	16

[a]Unilateral and bilateral cataracts (all types) or Y-suture opacities
[b]Unilateral and bilateral complete, diffuse posterior subcapsular, anterior polar or sutural cataracts
*$p < 0.05$ and > 0.01 (Fisher's Exact Test without Bonferoni Inequality, one-tailed)

Historical control data for lens disorders and cataracts diagnosed by Dr. Moore from Monsanto's EHL historical data base or control groups of studies are shown below.

EHL Historical Control Incidences of Pertinent Lens Abnormalities (Includes Unilateral and Bilateral Cataracts (all types, including Sutural) as Determined by Dr. Moore in CD Rats)

		Males			Females		
Study	Exam Date	No. Observed	No. Affected	% Affected	No. Observed	No. Affected	% Affected
1	07/83	37	0	0	38	0	0
2	02/85	22	3	14	17	2	12
3	09/85	30	10	33	24	6	25
4	11/85	17	2	12	25	3	12
5	04/86	11	1	9	16	1	6
6	09/88	12	2	17	29	1	3

The mean prevalence for males is 14.2 percent with a range of 0 to 33 percent. Dr. Rubin's evaluation showed the high-dose males to be beyond the range of EHL historical controls.

Both Dr. Moore and Dr. Rubin concluded that the occurrence of cataracts in the high-dose group may be compound-related.

Histopathological evaluation by an EHL pathologist of terminally sacrificed male rats showed the following cataract incidences: control, 2/14; low-dose, 3/19; mid-dose, 3/17; and high-dose, 5/17. There were no statistically significant differences.

For all animals on study, the EHL incidence of cataracts was control, 4/60; low-dose, 6/60; mid-dose, 5/60; and high-dose, 8/60. Again, there were no statistically significant differences.

EPL pathologist Dr. Larry Ackerman also examined all slides of eyes of all male rats on study. Dr. Ackerman's results are summarized below.

ACKERMAN (EPL)

Group	Animals Examined	Animals With Lens Abnormalities[a]	% Animals With Lens Abnormalities[a]
MN	60	3	5
M1	60	4	7
M2	60	4	7
M3	60	8	13
[illegible]	60	0	0
F1	60	0	0
F2	60	2	3
F3	60	2	3

aUnilateral and bilateral basophilic degeneration of major cataracts.

There are no significant ditferences in Dr. Ackerman's findings.

In summary, based on the ophthalmic examinations, the NOEL for cataracts and degenerative lens changes is the mid-dose level of 8000 ppm.

5. Blood was collected before treatment and at 6, 2, 18, and 24 months for hematology and clinical analysis from 10/sex/ group animals. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Total plasma protein (TP)
X	Hemoglobin (HGB)*	X	Leukocyte differential count
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)*	X	Mean corpuscular HGB conc. (MCHC)
X	Platelet count*	X	Mean corpuscular volume (MCV)
X	Reticulocytes		

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

Results - There were no compound-related hematological findings or changes that were considered toxicologically significant. Most of the statistically significant changes observed were usually small in magnitude, and were not consistent or dose-related.

b. Clinical Chemistry

X	Electrolytes:	X	Other:
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphorus*	X	Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	Enzymes:	X	Total bilirubin*
X	Alkaline phosphatase	X	Direct bilirubin
	Cholinesterase	X	Total protein
	Creatinine phosphokinase*		Triglycerides
	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

Results - There were no compound-related clinical chemistry findings or changes that were considered toxicologically significant. Most of the statistically significant changes were small and were not consistent or dose-related. At 24 months, there was a statistically significant increase in alkaline phosphatase in high-dose females (187% of control values) in comparison to controls. This is due to animal number F3053 which had a value of 490 IU/L. When this animal is not counted, the high-dose group is no longer statistically significant. Evaluation of the histopathological results of F3053 showed the following tumors: pheochromocytoma, adenocarcinoma (metastatic to the lung) of mammary gland, as well as a mammary gland adenoma, adenofibroma, and fibroma. Other nonneoplastic lesions were also present in the liver, heart, and kidneys.

6. Urinalysis - Urine was collected from fasted animals at 6, 12, 18, and 24 months on 10 sex/group of fasted animals. The CHECKED (X) parameters were examined.

X		X	
X	Appearance*	X	Glucose*
	Volume	X	Ketones*
	Specific gravity*	X	Bilirubin*

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

X	pH	X	Blood*
X	Sediment (miroscopic)*		Nitrate
X	Protein*	X	Urobilinogen

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

Results - A statistically significant increase in urine specific gravity (1.043 in controls vs. 1.061* ($p < 0.05$) in high-dose) and decrease in urine pH (6.9 in controls vs. 6.0 at high-dose) was observed in high-dose males at 6 months. Additionally, high-dose males showed statistically significantly decreased urinary pH at the 18- and 24-month sampling periods. The authors stated that this may have been related to the renal excretion of glyphosate which is a weak acid. However, since female rats did not display this finding, this explanation is not totally valid.

18 Months	pH
Control	6.8
High-Dose	5.8**
24 Months	
Control	6.4
High-Dose	5.7*

*$p < 0.05$
**$p < 0.01$

The NOEL for urinalysis is 8000 ppm.

7. Sacrifice and Pathology - All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X	Digestive System	X	Cardiovasc./Hemat.	X	Neurologic
	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	X	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*		

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

X	Duodenum*	X	Spleen*	X	Pituitary*
X	Jejunum*	X	Thymus*	X	Eyes (optic n.)*
X	Ileum*		Urogenital		Glandular
X	Cecum*	XX	Kidneys*	X	Adrenals*
X	Colon*	X	Urinary bladder*		Lacrimal gland
X	Rectum*	XX	Testes*	X	Mammary gland*
XX	Liver*	XX	Epididymides	X	Parathyroids*
	Gallbladder*	XX	Prostate	X	Thyroids*
X	Pancreas*	X	Seminal vesicle		Other
	Respiratory	X	Ovaries	X	Bone*
X	Trachea*	X	Uterus*	X	Skeletal
	muscle*				
X	Lung*			X	Skin
X	Nasal turbinates			X	All gross lesions all masses
				X	Harderian gland

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

Results

a. Organ Weight

12 Months - Relative to body weight, liver weight was statistically significantly increased in high-dose males.

Dose	Relative Weight Liver (%)	Percent Controls
Control	2.4082	
Low	2.5166	104
Mid	2.5269	105
High	2.7122*	113

*$p < 0.05$

Terminal Sacrifice - High dose males had statistically significantly increased absolute liver weight and liver weight relative to brain weight in comparison to controls.

Absolute Liver Weight (g)			Percent Liver Weight Relative to Brain Weight		
Dose		% Control	Dose		% Control
Control	16.5051		Control	707.2950	
Low	17.9773	109	Low	783.4629	111
Mid	17.8834	107	Mid	753.2652	106
High	18.6139*	113	High	805.0906*	114

*p < 0.05

The NOEL for organ weights is 8000 ppm.

b. Gross Pathology - There were no compound-related gross necropsy findings at the interim sacrifice, terminal sacrifice, or in animals dying on study.

c. Microscopic Pathology - (Age-adjusted, statistical analyses by statisticians of SACB are attached.)

1) Nonneoplastic - Mid-level females had a statistically significant increased incidence of inflammation of the gastric squamous mucosa. The findings for both sexes, as presented in the report, is shown below.

			Number of Lesions/Number Examined Incidence (%)			
Organ/Lesion	Sex	Dose (ppm):	0	2000	8000	20000
Stomach						
Inflammation						
Squam. Mucosa	M		2/58 (3)	3/58 (5)	5/59 (8)	7/59 (12)
	F		0/59 (0)	3/60 (5)	9/60* (15)	6/59 (10)

p ≤ 0.01; Fisher Exact Test with Bonferroni Inequality.

There was no increase in severity of the grade of the lesion with dose in either sex.

Historical control data from EHL are provided below.

Stomach	Inflammation, Squamous mucosa	Female	1	02/85	23	60	2	3.3
			2	10/85	24	70	3	4.3
			3	06/88	24	60	0	0.0
			4	09/88	24	59	1	1.7
			5	01/89	24	60	8	13.3
			6	03/89	24	58	5	8.6

Since the lesion is not dose-related, was not increased in severity with dose, is within the range of historical controls, at the high-dose, and occurred in only two (one mid-dose female (F2014) and one high-dose male (M3002)) terminally sacrificed animals (Note: this means that the lesion occurred a total of 33 incidences in rats which did not reach terminal sacrifice), the lesion is not considered compound-related.

2) Neoplastic

1. Pancreas - Low-dose males had a statistically significant incidence of pancreatic islet cell adenomas. The incidences of both sexes are shown below.

Organ/Lesion	Sex	Dose (ppm): 0	2000	8000	20,000
		Incidence (%)			
PANCREAS (Islet Cell)					
Hyperplasia	M[a]	2/58 (3) NS	0/57 (0)	4/60 (7)	2/59 (3)
	P[a]	4/60 (7)	1/60 (2)	1/60 (2)	0/59 (0)
Adenoma	M[a]	1/58 (2) NS	8/57* (14)	5/60 (8)	7/59 (12)
	P[a]	5/60 (8) NS	1/60 (2)	4/60 (7)	0/59 (0)
Carcinoma	M[a]	1/58 (2) NS	0/57 (0)	0/60 (0)	0/59 (0)

[a]All deaths considered
*$p \leq 0.05$; Fisher Exact Test with Bonferroni Inequality
NS = Not significant; Peto Test ($p \leq 0.05$)
NA = Peto Test not performed

Organ/Lesion	Sex	Dose (ppm):	Incidence (%) 0	2000	8000	20,000
	P[a]		0/60 (0) NA	0/60 (0)	0/60 (0)	0/59 (0)
Adenoma, Carcinoma Combined	M[a]		2/58 (3) NS	8/57 (14)	5/60 (8)	7/59 (12)
	F[a]		5/60 (8) NS	1/60 (2)	4/60 (7)	0/59 (0)

[a]All deaths considered
*$p \leq 0.05$; Fisher Exact Test with Bonferroni Inequality
NS = Not significant; Peto Test ($p \leq 0.05$)
NA = Peto Test not performed

Historical control data from Monsanto's EHL are shown below.

EHL 87122 - Historical Control Information for Histopathological Findings (All Deaths)

Organ	Lesion	Sex	Study	Terminal Necropsy Date	Months of Study	No. Observed	No. Affected	% Affected
Pancreas	Islet Cell Adenoma	Male	1	07/83	24	68	2	2.9
			2	02/85	23	59	5	8.5
			3	10/85	24	69	4	5.8
			4	06/85	24	57	1	1.8
			5	09/88	24	60	5	8.3
			6	01/89	24	60	3	5.0
			7	03/89	24	59	3	5.1

It can be seen from the study results that the incidences of the pancreatic islet cell adenomas at the low- and high-dose group exceed the historical control range of 1.8 to 8.5 percent. However, there is no dose-response relationship in the occurrence of these tumors in males, no progression to carcinoma, and the incidence of hyperplasia is not dose-related.

In a 1981 Lifetime (26 Months) Feeding Study in Rats with Glyphosate (Bio/dynamics Project No. 77-2062), the incidences of islet cell pancreatic tumors were as follows:

Dose (mg/kg/day)	Sex	0	3	10	30
Hyperplasia	M	3/58 (6)	2/49 (4)	1/50 (2)	0/50 (0)
	F	2/50 (4)	1/50 (2)	0/50 (0)	0/50 (0)
Adenoma	M	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
	F	2/50 (4)	1/50 (2)	1/50 (2)	0/50 (0)
Carcinoma	M	0/50 (0)	0/50 (0)	0/50 (0)	1/50 (2)
	F	0/50 (0)	1/50 (2)	1/50 (2)	1/50 (2)
Adenoma/Carcinoma Combined	M	0/50 (0)	5/50 (10)	2/50 (4)	3/50 (6)
	F	2/50 (4)	2/50 (4)	2/50 (4)	1/50 (2)

These finding were not considered compound-related effects in this study; the combined incidence of pancreatic islet cell adenoma and carcinoma in males was 0, 10, 4, and 6 in the control, low-, mid-, and high-dose groups, respectively. In females, the combined incidence was 4, 4, 4, and 2 in control, low-, mid-, and high-dose groups, respectively. Shown below are the 1981 and 1990 studies combined.

Pancreatic Islet Cell Tumors

			% Incidence Males				
Dose (mg/kg/day)	0	3	10	30	90	360	940
No. Examined	118	49	50	50	57	60	59
Hyperplasia	5	2	1	0	0	7	3
%	(4)	(4)	(2)	(0)	(0)	(12)	(5)
Adenoma	1	5	2	2	8	5	7
%	(1)	(10)	(4)	(4)	(14)	(8)	(12)

	% Incidence						
	Males						
Dose (mg/kg/day)	0	3	10	30	90	360	940
Carcinoma	1	0	0	1	0	0	0
%	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Adenoma/Carcinoma Combined	2	5	2	3	8	5	7
%	(2)	(10)	(4)	(6)	(14)	(8)	(12)

The incidence of pancreatic islet cell tumors for the two studies does not show a dose-related increase in adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%).

Open literature information (data attached) provided by Monsanto from other laboratories shows a prevalence up to 17.0 percent in untreated Sprague-Dawley rats.

Due to the high incidence of islet cell pancreatic adenomas in each male treated group, in comparison to concurrent controls, TB-I recommends that the HED Peer Review Committee review the oncogenic potential of glyphosate with respect to this tumor type.

2. Thyroid - C-cell adenomas were slightly increased in male and female mid- and high-dose groups as shown below.

Thyroid C-Cell Lesions

Sex/Lesion	Incidence (%) 0 ppm	2000 ppm	8000 ppm	20,000 ppm	Monsanto's EHL Historical Control Range %
			Males		
Hyperplasia	5/60 (8.3)	1/58 (1.7)	6/58 (10.3)	5/60 (8.3)	4.3 - 20
Adenoma	2/60 (3.3)	4/58 (6.9)	8/58 (13.8)	7/60 (11.7)	1.8 - 10.6
Carcinoma	0/60 (0)	2/58 (3.4)	0/58 (0)	1/60 (1.7)	0 - 5.2

Thyroid C-Cell Lesions

Sex/Lesion	Incidence (%) 0 ppm	2000 ppm	8000 ppm	20,000 ppm	Monsanto's EHL Historical Control Range %
			Females		
Hyperplasia	10/60 (16.7)	5/60 (8.3)	9/60 (15)	5/60 (8.3)	4.3 - 16.9
Adenoma	2/60 (3.3)	2/60 (3.3)	6/60 (10)	6/60 (10)	3.3 - 10
Carcinoma	0/60 (0)	0/60 (0)	1/60 (1.7)	0/60 (0)	0 - 2.9

Since there was no dose-response in adenomas in either sex, no progression to carcinoma in a dose-related manner, no significant dose-related increase in severity of grade or incidence in hyperplasia, and in light of historical controls adenomas, the C-cell adenomas in males and females are not considered compound related.

3. Liver

Males - There was a slight dose-related increase in hepatocellular adenomas in males but the incidence was within the range of historical controls from Monsanto's EHL.

Hepatocellular Neoplasms in Males

Lesion	Incidence (%)[a] 0 ppm	2000 ppm	8000 ppm	20,000 ppm	Monsanto's EHL Historical Control Range
Adenoma	2/60 (3.3)	2/60 (3.3)	3/60 (5.8)	7/60 (11.7)	1.4 - 18.3
Carcinoma	3/60 (5)	2/60 (3.3)	1/60 (1.7)	2/60 (3.3)	0 - 6.7

Nonneoplastic liver lesions are shown below.

Hepatocellular Lesions in Males

Lesion	Incidence (%) 0 ppm	2000 ppm	8000 ppm	20000 ppm	Monsanto's EHL Historical Control Range
Hyperplasia	0/60	0/60	1/60 (1.7)	1/60 (1.7)	Not Available[a]
Focus of Cell Alteration	23/60 (38)	20/60 (33)	29/60 (48)	27/60 (45)	13.3 - 45.6
Centrilobular Necrosis	4/60 (6.7)	5/60 (8.3)	3/60 (5.0)	4/60 (6.7)	Not Available

[a]Could not be determined because hyperplasia and hypertrophy were combined for some studies in historical control data base.

As can be seen from the hepatocellular tumor data, the historical controls, and the nonneoplastic liver lesions data, there is no progression from adenoma to carcinoma and the nonneoplastic lesions (hyperplasia, centrilobular necrosis, and focus of cell alteration) do not show a compound-related effect. Therefore, the slightly increased occurrence of hepatocellular adenomas in males is not considered compound-related.

Attachment

R:62826:Dykstra:C.Disk:KEVRIC:04/26/91:aw:EK:CL
R:62894:Dykstra:C.Disk:KEVRIC:05/10/91:aw

Caswell 661A

(37)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

MEMORANDUM APR 3 1985 WASHINGTON, D.C. 20460

008527

SUBJECT: Glyphosate; EPA Reg.#: 524-308; mouse oncogenicity study
Caswell #: 661A
Accession #: 251007-014

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: Robert Taylor
Product Manager (25)
Registration Division

4/1/85

THUR: Robert P. Zendzian, Ph.D.
Acting Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: William Dykstra, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

3/29/85

4/2/85

Conclusions:

1. Glyphosate was oncogenic in male mice causing renal tubule adenomas, a rare tumor, in a dose-related manner. The study is acceptable as core-minimum data.

2. The information on the oncogenicity of glyphosate was evaluated by a Toxicology Branch AD Hoc Committee which concluded that this was an oncogenic response. A copy of the consensus report of the committee is attached.

Review:

1. A chronic feeding study of Glyphosate in mice (Biodynamics # BDN-77-420; Project No. 77-2061; 7/21/83).

Test Material:

Glyphosate technical, purity = 99.7%; fine, white clumped powder; lot number, NB178260813; NB178261017.

Groups of 50 male and 50 female randomized CD-1 mice, individually caged, were administered diets containing 0, 1000, 5000, and 30,000 ppm of test material for 24 months.

Parameters evaluated were toxic signs, mortality, body weight, food consumption, water consumption and hematology at 12, 18 and 24 months.

All animals were necropsied and selected organs were weighed. Tissues were stained in H and E and examined microscopically.

Statistical analyses of the data were performed.

Results:

No treatment-related toxic signs were noted during the study. Mortality was low during the first 18 months of the study as shown in the table below as reported:

Cumulative Mortality

DOSE	Males			Females		
(ppm)	12 Mo	18 Mo	24 Mo	12 Mo	18 Mo	24 Mo
0	9	12	30	3	15	30
1,000	9	19	34	4	16	38
5,000	7	14	33	1	8	23
30,000	4	11	24	5	13	27

Body weight was consistently decreased for males and to a lesser extent, females at the 30,000 ppm dosage level during the study at several sampling intervals. Changes in body weight at the low- and mid-dose group were variable and not dose-related.

Food consumption showed no compound-related or dose-related effect. Hematological values although significant in some instances did not show a consistent dose-related response.

Necropsy did not show treatement-related lesions. There was good correlation between gross and microscopic findings. The relative and absolute weight of the testes and ovaries were increased in high dose males and females, but no histopathological finding was present as a underlying factor.

Renal tubule adenomas occurred in male mice in the following manner as reported:

Dose (ppm)	0	1,000	5,000	30,000
Number examined	49	49	50	50
Renal tubule adenoma	0	0	1	3

They occurred in male mice 4029, 4032 and 4041 of the high-dose, and male 3023 of the mid-dose group and all were unilateral.

These tumors are rare, dose related and considered compound-related. These tumors were present at terminal kill.

Other neoplasmas were considered unrelated to treatment. No effect on latency was noted.

Significant trends and significant high-dose effects were observed in non-neoplastic lesions. The lesions considered treatment-related were hepatocyte hypertrophy, central lobular hepatocyte necrosis and chronic interstitial nephritis in high-dose males and proximal tubule epithelial basophilia and hypertrophy in high-dose females.

The table below shows the incidence of these lesions as reported:

	Control	Low	Mid	High	Linear Trend
Central lobular hepatocyte hypertrophy					
- males	9/49	5/50	3/50	17/50	b
- females	3/49	5/50	5/50	1/49	
Central lobular hepatocyte necrosis					
- males	0/49	2/50	2/50	10/50[a]	b
- females	2/49	1/50	4/49	2/49	
Chronic interstitial nephritis					
- males	5/49	2/49	7/50	12/50	b
- females	4/50	8/50	2/50	4/50	
Proximal tubule epithelial basophilia and hypertrophy					
- males	15/49	10/49	15/50	7/50	
- females	0/50	2/50	4/50	9/50[a]	a

[a]Statistically significant increase compared to control ($p \leq 0.01$) using the Chi-Square test (uncorrected for continuity).

[b]Statistically significant linear trend ($p \leq 0.01$) using the Cochran-Armitage test.

Conclusion:

Glyphosate was oncogenic in male mice producing a dose-related increased in renal tubule adenomas, a rare tumor. Dose-related non-neoplastic lesions occurred in both sexes. The NOEL for systemic effects was 5000 ppm. At the LEL, 30,000 ppm, there were increased hepatocyte hypertrophy, hepatocyte necrosis and interstitial nephritis in male mice and an increased incidence of proximal tubule epithelial basophilia and hypertrophy in female mice. Additionally, there were decreased body weights in male and female mice at 30,000 ppm which are considered compound-related.

Classification:

Core minimum data.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

008527

008527

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject. Glyphosate, Qualitative Risk Assessment -
2-Year Sprague-Dawley Rat Dietary Study

Caswell no.66A

From Bernice Fisher, Biostatistician
Science Support & Special Review Section
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

Bernice Fisher 5/2/91

To. William Dykstra, Ph.D., Pharmacologist
Review Section I
Toxicology Branch I - Insecticide/Rodenticide Support
Health Effects Division (H7509C)

Thru: Esther Rinde, Ph.D., Acting Section Head
Science Support & Special Review Section
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

E. Rinde 5/2/91

The qualitative risk assessment of glyphosate was based upon a 2-year dietary study of Sprague-Dawley rats.

The attached tables present in tabular form, the results of the statistical analysis of data from the dietary study of Sprague-Dawley rats (MSL 10495, R.D.no. 1014, Project no. 0-2037).

The sponsor of the study was Monsanto Agricultural Company The study was completed and issued in September, 1990.

Table 1. Glyphosate - Sprague-Dawley Rat Study, Male Mortality Rates[+] and Cox or Generalized K/W Test Results[++]

	Weeks					
Dose (ppm)	1-26	27-53	54[a]	54-78	79-105[b]	Total
0	1/60	4/58[c]	10/54	8/44	22/36	35/49(71)
2000	1/60	4/59	10/55	7/45	19/38	31/50(62)
8000	0/60	1/60	10/59	7/49	25/42	33/50(66)
20000	0/60	2/60	10/58	6/48	25/42	33/50(66)

[+] Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[++] Thomas, D.G., Breslow, N. and Gart, J.J. - Trend and Homogeneity Analysis of Proportions and Life Table Data, version 2.0.

( ) percent

[a] Interim sacrifice at week 54.
[b] Final sacrifice at week 105.
[c] excludes an accidental death - one animal at week 53.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.
If * then $p<.05$ and if ** then $p<.01$.

Table 2. Glyphosate - Sprague-Dawley Rat Study, Female Mortality Rates[+] and Cox or Generalized K/W Test Results[++]

	Weeks					
Dose (ppm)	1-26	27-53	54[a]	54-78	79-105[b]	Total
0	0/60	3/60	10/57	9/47	16/38	28/50(56)
2000	0/60	0/60	10/60	10/50	18/40	28/50(56)
8000	0/60	1/60	10/59	14/49	18/35	33/50(66)
20000	2/60	3/58	10/55	7/45	20/38	32/50(64)

[+] Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[++] Thomas, D.G., Breslow, N. and Gart, J.J. - Trend and Homogeneity Analysis of Proportions and Life Table Data, version 2.0.

( ) percent

[a] Interim sacrifice at week 54.
[b] Final sacrifice at week 105.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.
If * then $p<.05$ and if ** then $p<.01$.

Table 3. Glyphosate - Sprague-Dawley Male Rats, Hepatocellular Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors	0	2000	8000	20000
Carcinomas (%)	3/44 (7)	2/45 (4)	1/49 (2)	2[a]/48 (4)
p=	0.324	0.489(n)	0.269(n)	0.458(n)
Adenomas (%)	2/44 (5)	2/45 (4)	3/49 (6)	7/48 (15)
p=	0.016*	0.683(n)	0.551	0.101
Both (%)	5/44 (11)	4/45 (9)	4/49 (8)	9/48 (19)
p=	0.073	0.486(n)	0.431(n)	0.245
Hyperplasia only (%)	0/44 (0)	0/45 (0)	1[c]/49 (2)	0/48 (0)
p=	0.462	1.000	0.527	1.000

+ Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

(n) negative change from control

[a] First carcinoma observed at week 85, dose 20000 ppm.
[b] First adenoma observed at week 88, dose 20000 ppm.
[c] hyperplasia observed at week 89, dose 8000 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level;
If * then $p<.05$ and if ** then $p<.01$.

Table 4. Glyphosate - Sprague-Dawley Male Rats, Pancreatic Islet Cell Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors	0	2000	8000	20000
Carcinomas (%)	1[a]/43 (2)	0/45 (0)	0/49 (0)	0/48 (0)
p=	0.159	0.489(n)	0.467(n)	0.472(n)
Adenomas (%)	1/43 (2)	8/45 (18)	5/49 (10)	7[b]/48 (15)
p=	0.170	0.018*	0.135	0.042*
Both (%)	2/43 (5)	8/45 (18)	5/49 (10)	7/48 (15)
p=	0.241	0.052	0.275	0.108
Hyperplasia only (%)	2/43 (5)	0/45 (0)	3/49 (6)	2[c]/48 (4)
p=	0.323	0.236(n)	0.562	0.649(n)

+ Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacificed before week 55.

(n) negative change form control

[a] First carcinoma observed at week 105, dose 0 ppm.
[b] First adenoma observed at week 81, dose 20000 ppm.
[c] First hyperplasia observed at week 91, dose 20000 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.
If * then p<.05 and if ** then p<.01.

Table 5. Glyphosate - Sprague-Dawley Male Rats, Thyroid C-Cell Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose(ppm)			
Tumors	0	2000	8000	20000
Carcinomas	0/54	2[a]/55	0/58	1/58
(%)	(0)	(4)	(0)	(2)
p=	0.452	0.252	1.000	0.518
Adenoma	2[b]/54	4/55	8/58	7/58
(%)	(4)	(7)	(14)	(12)
p=	0.069	0.348	0.060	0.099
Both	2/54	6/55	8/58	8/58
(%)	(4)	(11)	(14)	(14)
p=	0.077	0.141	0.060	0.060
Hyperplasia only	4/54	1/55	5[c]/58	4/58
(%)	(7)	(2)	(9)	(7)
p=	0.312	0.176(n)	0.546	0.601

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before week 54.

(n) negative change from control

[a] first carcinoma observed at week 86, dose 2000 ppm.
[b] first adenoma observed at week 54, dose 0 ppm.
[c] first hyperplasia observed at week 54, dose 8000 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.
If * then $p<.05$ and if ** then $p<.01$.

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Table 6. Glyphosate - Sprague-Dawley Female Rats, Thyroid C-Cell Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose(ppm)			
Tumors	0	2000	8000	20000
Carcinomas (%)	0/57 (0)	0/60 (0)	1[a]/59 (2)	0/55 (0)
p=	0.445	1.000	0.509	1.000
Adenomas (%)	2/57 (4)	2/60 (3)	6[b]/59 (10)	6/55 (11)
p=	0.031*	0.671(n)	0.147	0.124
Both (%)	2/57 (4)	2/60 (3)	7/59 (12)	6/55 (11)
p=	0.033*	0.671(n)	0.090	0.124
Hyperplasia only (%)	10[c]/57 (18)	5/60 (8)	7/59 (12)	4/55 (7)
p=	0.113	0.112(n)	0.274(n)	0.086(n)

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before 54 weeks.

(n) negative change from control

[a] First carcinoma observed at week 93, dose 8000 ppm.
[b] First adenoma observed at week 72, dose 8000 ppm.
[c] First hyperplasia observed at week 54, dose 0 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.
If * then $p<.05$ and if ** then $p<.01$.

Bill Dykstra 0085

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 24 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Transmittal of the Final FIFRA Scientific Advisory Panel Reports on the February 11-12, 1986 Meeting

TO: Steven Schatzow, Director
Office of Pesticide Programs (TS-766)

The above mentioned meeting of the FIFRA Scientific Advisory Panel (SAP) was an open meeting held in Arlington, Virginia to review the following topics:

(1) A set of scientific issues being considered by the Agency in connection with the Registration Standard for Glyphosate;

(2) A set of scientific issues in connection with the Agency's proposed action on the non-wood uses of Pentachlorophenol as set forth in the Position Document 4;

(3) A set of scientific issues being considered by the Agency in connection with the Registration Standard for Oryzalin;

(4) A set of scientific issues being considered by the Agency in connection with the Registration Standard for Amitraz;

(5) A set of scientific issues being considered by the Agency in connection with the Registration Standard for Acephate;

(6) A set of scientific issues being considered by the Agency in connection with Subdivision U of the Pesticide Assessment Guidelines.

Please find attached the SAP's final reports on the six issues discussed at the meeting.

Stephen L. Johnson, Executive Secretary
FIFRA Scientific Advisory Panel (TS-769)

Attachments

cc: Panel Members
John A. Moore
James Lamb
Al Heier
Susan Sherman
John Melone
Douglas Campt
EPA Participants

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FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Registration Standard for Glyphosate

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of the data base supporting the Environmental Protection Agency's (EPA) decision to classify Glyphosate as a class C (possible human) carcinogen. The review was conducted in an open meeting held in Arlington, Virginia, on February 11, 1986. All Panel members, except Dr. Thomas W. Clarkson, were present for the review. In addition, Dr. David Gaylor, Director of the Biometry Staff at the National Center for Toxicological Research, served as an ad hoc member of the Panel.

Public notice of the meeting was published in the Federal Register on Friday, January 17, 1986 (Citation 51-FR2568).

Oral statements were received from staff of the Environmental Protection Agency and from Mr. Robert Harness and Dr. Timothy Long of Monsanto Company.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF SAP RECOMMENDATIONS

General Comments on Carcinogen Classification

The Panel concurs that it is necessary to categorize chemicals as to their apparent carcinogenic risk to man. The Panel is concerned that the categories outlined in the Agency's Cancer Guidelines are somewhat limited in scope. For only a small number of specific chemicals is there epidemiologic evidence of their carcinogenicity in man, either sufficient evidence (Group A) or limited evidence (Group B-1). Thus, most chemicals that are carcinogenic for animals have been placed in Groups B-2 and C. Category D has apparently not been used. The Panel urges the Agency to attempt to develop a more discriminatory classification scheme.

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Glyphosate

The Agency requested the Panel to focus its attention upon a set of issues relating to the pesticide Glyphosate. There follows a list of the issues and the SAP's response to each question.

1. Based on the Agency's weight of the evidence assessment with emphasis on the mouse kidney tumors, the Agency has classified Glyphosate as a class C (possible human) carcinogen. The Agency specifically requests any comment that the Panel may wish to present with regard to its assessment of the weight of evidence and subsequent determination of carcinogenicity according to the Agency's Cancer Guidelines.

2. The Agency requests also that the Panel consider what weight should be given to this marginal increase in kidney tumors, the importance of this type of tumor in the assessment of the carcinogenicity of Glyphosate, and the weight given to historical and concurrent controls for this type of evaluation.

Panel Response:

In the instance of Glyphosate, the Panel concurs that the data on renal tumors in male mice are equivocal. Only small numbers of tumors were found in any group, including those at the highest dose which appear to have exceeded the maximal tolerated dose. The vast majority of the pathologists, who examined the proliferative lesion in the male control animal, agreed that the lesion represented a renal adenoma. Therefore, statistical analysis of the data should utilize this datum. In addition, the statistical analysis shall be age-adjusted; when this is done, no oncogenic effect of Glyphosate is demonstrated using concurrent controls. Nevertheless, the occurrence of three neoplasms in high dose male mice is unusual and using historical controls is statistically highly significant. Furthermore, categorization of the oncogenic risk of Glyphosate is complicated by the fact that doses used in the rat study do not appear to have reached the maximal tolerated dose. Under these circumstances, the Panel does not believe that it is possible to categorize Glyphosate clearly into Group C (possible human carcinogen) or Group E (no evidence of carcinogenicity for humans). The Panel proposes that Glyphosate be categorized as Group D (not classified) and that there be a data call-in for further studies in rats and/or mice to clarify unresolved questions.

Regarding the issue of using historical or concurrent controls, the Panel believes that this has to be decided on a case-by-case basis. For Glyphosate, the historical control data support that there may be reason for concern. However, the level of concern raised by historical control data was not great enough to displace putting primary emphasis on the concurrent controls.

008527
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FOR THE CHAIRMAN

Certified as an accurate report of Findings:

Stephen L. Johnson
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 2/24/86

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

07252

JUN 19 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate - EPA Registration Nos. 524-318 and 524-333 - Historical Control Data for Mouse Kidney Tumors

MRID No.: 00130406
Caswell No.: 661A
Record No.: 238,412
Project No.: 9-0697

FROM: William Dykstra, Reviewer
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

William Dykstra 6/7/89

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

THRU: Edwin Budd, Acting Branch Chief
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

Budd 6/9/89

and

William Burham, Deputy Director
Health Effects Division (H7509C)

W. Burham 6/9/89

Requested Action

Review historical control data on mouse kidney tumors submitted by Monsanto in response to meeting of November 10, 1988.

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Conclusions and Recommendations

The historical control data showed that the incidence of renal neoplasms in male CD-1 mice ranged from 0 to 3.3 percent at Bio/dynamics (the laboratory that performed the glyphosate mouse oncogenicity study), 0 to 4.7 percent at Hazleton, 0 to 1.7 percent at IRDC, 0 to 3.3 percent at Litton Bionetics, and 0 to 1.4 percent in Japan (Japanese Institute for Environmental Toxicology). The range of incidences of 0 to 7.1 percent reported by Monsanto in their November 10, 1988 meeting with the Agency was taken from the data on F_1 male mice in reproduction studies at Hazleton.

These F_1 data could not be further substantiated by Monsanto and therefore, cannot be used to support the Monsanto position.

Other data study presented by Monsanto, briefly, were two chronic bioassays with male CD-1 mice in which the following incidences of renal neoplasms were noted:

	Control	Low	Mid	High
Study I	0/80	2/80	1/80	2/80
Study II	2/50	1/50	3/50	3/50

Monsanto cites these data as showing an incidence of 0 to 6 percent in control or treated groups (the occurrences of renal tumors in treated groups were not considered compound-related) which matches the upper incidence of 6 percent in the glyphosate study. Toxicology Branch (TB) does not consider these random data as convincing.

However, based on a meeting held June 7, 1989 between W. Dykstra, E. Budd, and W. Burnam, TB concludes that a repeat of the mouse oncogenicity study is not required at this time. After the results of the new 2-year rat chronic toxicity and oncogenicity study are reviewed, TB will reconsider whether the repeat of the mouse oncogenicity study is required.

Background

On November 10, 1988, a meeting was held between EPA staff and representatives of Monsanto to discuss the Agency's requirement that the mouse oncogenicity study with glyphosate be repeated (memorandum attached).

Monsanto stated that there were historical control data demonstrating that the incidence of mouse kidney neoplasms ranged from 0 to 7.1 percent. This incidence exceeded the incidence of 6 percent from the high-dose group in the glyphosate study. Monsanto indicated that a repeat mouse oncogenicity study was not required.

EPA stated that the historical control data should be submitted in order to reevaluate the Agency's position on the repeat study.

In response to this request, Monsanto has submitted historical control data from several sources to substantiate their contention regarding the range of mouse kidney tumor neoplasms.

Review

1. The incidence of renal tubule tumors in the glyphosate mouse study is shown below:

	Mouse Kidney			
Dose (ppm)	0	1000	5000	30,000
No. Examined	49	49	50	50
Tubular Adenomas	1	0	1	3
Percent Incidence	2%	0%	2%	6%

2. The historical control data are presented below and are also attached to this memorandum.

   a. Bio/dynamics Historical Control Data - From studies initiated between 1976 and 1980 and terminated between 1978 and 1982, the incidence of tumors is shown below as submitted by Monsanto:

CD-1 COBS (ICR Derived) Mice
Bio/dynamics, Inc.
MALES - KIDNEYS

008527

CONTROL DATA

STUDY I.D.	A	B	C	D	E	F	G	H*	I	J**	K+	L	M**	N	O	P
Tissue/Finding																
No. Examined	111	121	104	119	120	120	120	15	50		47	49		200	50	60
NEOPLASTIC FINDINGS																
B-Tubular Adenoma	1				2											
M-Tubular Carcinoma																

B = benign; M = malignant.
Control groups IA and IB counted together.
+ Study K = common control animals used for two test articles.
* = Gross Lesions only - kidney not routinely examined.
** = No microscopic findings recorded to date.

Note: Search for Renal Tubular Carcinomas revealed no incidence in these studies.

Male Charles River CD-1 Mice
Bio/dynamics, Inc.
KIDNEY

CONTROL DATA

STUDY I.D.	A		B		C		D		E		F		G	
	*	**	*	**	*	**	*	**	*	**	*	**	*	**
Tissue/Finding														
Neoplasm														
No. Examined	57	54	61	51	53	59	60	60	60	60	60	60	60	60
B - Tubular Adenoma		01								02				

*Control Group A	Start	6/78	12/77	12/77	10/78	11/78	11/77	10/77
**Control Group B	Terminate	7/80	4/80	3/80	4/81	4/81	4/80	4/80

Discussion

It can be seen from the above data that the range of historical controls of mouse renal neoplasms from Bio/dynamics is 0 to 3.3 percent. It should be noted that the glyphosate mouse oncogenicity study was conducted by Bio/dynamics between 1980 and 1982. Therefore, the 6 percent incidence of renal tumors in the high-dose group in the glyphosate mouse study exceeds the upper limit of the range of 3.3 percent in the historical

b. Hazleton's Historical Control Data

In a letter dated December 2, 1989 from J.M. Burns of Hazleton to D. Ward of Monsanto, six studies are cited as shown below:

The incidences are for scheduled sacrifices and unscheduled deaths combined.

Study	Type	Init.	Term.	Tubular Cell Carcinoma, Males
1	Dietary	3/80	3/82	2/43
2	Dietary	4/80	4/82	1/100
3	Dietary	9/81	9/83	0/80
4	Dietary	12/79	12/81	0/50
5	Dietary	5/82	5/84	0/60
6	Gavage	8/83	8/85	0/47

Tubular cell carcinomas only were observed.

Discussion

The range of mouse renal neoplasma cited by Hazleton is 0 to 4.7 percent. Therefore, the incidence of 6 percent in the high-dose group of the glyphosate mouse study exceeds the historical controls from Hazleton.

Additional, Monsanto has submitted "representative historical control data" from Hazleton reproduction studies in which renal neoplasia occurred in groups of F_1 generation control mice which were sacrificed after 91 to 105 weeks. These data are shown below:

NEOPLASIA IN CD-1® F_1 MICE - UNTREATED CONTROLS

FINDING	POSITIVE FINDINGS (MALES)	ANIMALS EXAMINED (MALES)
TISSUE NAME--KIDNEY		
TUBULAR CELL ADENOMA		
	1	15
	1	14
POSITIVE TOTALS	2	29
OVERALL TOTALS	2	56
OVERALL PERCENT	3.6	
RANGE OF PERCENTAGES	7	7
TUBULAR CELL CARCINOMA		
	1	15
POSITIVE TOTALS	1	15
OVERALL TOTALS	1	56
OVERALL PERCENT	1.8	
RANGE OF PERCENTAGES	7	7

Discussion

Apparently, this historical control data, which range from 0 to 7.1 percent, are the historical control data cited by Monsanto in their meeting with EPA on November 10, 1988. In a telephone communication on January 30, 1989 to Dr. Ward of Monsanto (314-694-8818), Dr. Ward indicated that Hazleton was unable to provide any additional details (dates of study, supplier, pathologists, etc.) about these particular historical controls. Therefore, in light of this telephone communication, TB concludes that these particular historical controls from F_1 male mice cannot be used to substantiate the Monsanto position.

C. IRDC Historical Control Data

Historical control data from IRDC on the incidences of renal neoplasms in CD-1 male mice in 19 studies of 24 to 25 month duration conducted between 1976 and 1978 are summarized below.

Tumors	No. Tumors	Range	No. Examined
Kidneys			1490
Adenoma	3	0-1.3	
Carcinoma	4	0-1.7	

Discussion

The range of 0 to 1.7 percent for renal neoplasms at IRDC does not exceed the incidence of 6 percent in the high-dose group of the glyphosate mouse study. The submitted historical control data from IRDC did not show the individual study incidences and therefore, is limited in this respect.

Spontaneous Renal Neoplasms Observed on 18 Food Color Additive Studies

Monsanto has submitted the incidence of renal neoplasms from 18 food color additive chronic studies with CD-1 mice (supplied to Monsanto by Dr. J.K. Haseman of NIEHS). These data are presented below:

INCIDENCE OF RENAL NEOPLASMS IN CONTROL MALE CD-1 MICE

Study ID[a]	Testing Laboratory[b]	Lesion Description	Incidence Group A	Group B
Blue No. 1	IRD	Cortical adenoma	0/60	1/60
Blue No. 2	B/d	Tubular cell adenoma	0/57	1/54
Green No. 3	B/d		0/51	0/53
Green No. 5	HL	Tubular cell adenoma	1/59	0/59
Yellow No. 5	IRD		0/60	0/60

a/A series of chronic bioassays in Charles River CD-1 mice were conducted on 18 food color additives. These studies were sponsored by the Certified Colors Manufacturers Association; the Cosmetic, Toiletries, and Fragrance Association; and the Pharmaceutical Manufacturers Association. Each study utilized 2 concurrent control groups of 60 mice/sex/group. These studies were conducted during the period of 1977 to 1980.

b/Testing laboratories were: International Research and Development Corporation (IRD); Bio/dynamics, Inc. (B/d); Hazleton Laboratories (HL); and Litton Bionetics (LB).

INCIDENCE OF RENTAL NEOPLASMS IN CONTROL MALE CD-1 MICE (Cont'd)

Study ID	Testing Laboratory	Lesion Description	Incidence Group A	Incidence Group B
Yellow No. 6	B/d		0/61	0/60
Yellow No. 10	B/d		0/60	0/60
Orange No. 5	B/d		0/60	0/60
Orange No. 17	B/d	Tubular cell adenoma	0/60	2/60
Red No. 3	IRD		0/60	0/60
Red No. 6	IRD		0/60	0/60
Red No. 9	LB	Tubular cell adenoma	0/59	2/60
Red No. 9		Tubular cell adenocarcinoma	1/59	0/60
		Cholesterol granuloma	1/59	0/60
Red No. 19	B/d		0/54	0/57
Red No. 21	IRD	Adenoma (N.O.S.)	1/60	0/60
Red No. 27	LB	Tubular cell adenoma	1/60	0/59
		Hemagiosarcoma	1/60	0/59
Red No. 30	HL		0/60	0/58
Red No. 33	IRD	Tubular cell adenoma	1/60	0/60
		Cortical carcinoma	1/60	0/60
Red No. 36	LB		0/60	0/60

Discussion

The incidence of renal tubular neoplasms ranged from 0 to 3.3 percent. It should be noted that the 3.3 percent incidonce (2/60) of tubular cell adenoma in Orange No. 17 from Bio/dynamics was previously reported by Monsanto as historical

control data by Bio/dynamics and does not represent additional findings. The incidence of 3.3 percent (2/60) for renal tubular cell adenoma in Red No. 9 from Litton Bionetics was not previously reported and is considered new data.

E. Historical Control Data in CD-1 Mice From The Institute of Environmental Toxicology (Tokyo, Japan).

The incidence of renal neoplasms from male CD-1 mice was 6/891 (0.67%). In a telephone communication on January 30, 1989 with Dr. Ward of Monsanto, Dr. Ward indicated that for individual studies the incidence of renal neoplasms ranged from 0 to 1.4 percent (1/70). The range of 0 to 1.4 percent of renal neoplasms is comparable to the incidences observed at other laboratories.

Attachments

R:53487:Dykstra:C.Disk:KENCO:2/6/89:CT:VO:CT
R:57213:Dykstra:C.Disk:KENCO:3/7/89:rw:vo:jh:dg

008527

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/SACB
TOX ONELINERS

TOXCHEM NO. 661A- N-(Phosphonomethyl)glycine FILE LAST PRINTED: 03/26/91

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	CORE GRADE/ DOCUMENT#
83-1(a) and 83-2(a) Feeding/oncogenic-2 year Species: rat IBT B-564, BTL 71-32; 1/14/74	Glyphosate Tech.	112789	IBT invalid		Invalid 000265 000262 000280
83-1(a) and 83-2(a) Feeding-26 months Species: rat Bio/dynamics Inc. 77-2062; 9/18/81	Glyphsoate Tech.	246617 246618 246619 246620 246621	Oncogenic NOEL > 31 mg/kg/day (HDT) Systemic NOEL > 31 mg/kg/day (HDT) Levels tested: 0, 3, 10, 31 mg/kg		Minimum 081425 082175 082666 Suppl. (enco) 004465
83-1(b) Feeding-2 year Species: dog IBT J-565 (651-00565); 11/30/73	Glyphosate Tech. (CP 67573 acid form)	112789 94161	Evaluation considering Canadian validation findings of 6/19/78 and additional data submitted by Monsanto on 7/2/82 and reclassified as IBT invalid		Invalid 000265 000269 002134
83-1(b) Feeding-1 year Species: dog Monsanto Environ. Health Lab 830116; ML-83-137; 8/22/85	Glyphosate Tech. 96.13%	260021	Systemic NOEL > 500 mg/kg/day. Doses: 0, 20, 100 & 500 mg/kg/day by capsule in beagle dogs.		Guideline 004975 Guideline 005651
83-2(b) Oncogenic-18 month Species: mice IBT B-569, BTL 71-3; 9/19/73	Glyphosate Tech.		IBT invalid		Invalid 000277
83-2(b) Oncogenic-2 year Species: mice Bio/dynamics Inc. 77-2061; 7/21/83	Glyphosate Tech. 99.7% Lot NB178260813 & NB178261017	251007 251008 251009 251014	Levels tested in CD-1 str.: 0, 1000, 5000, 30,000 ppm. Oncogenic potential undetermined based on SAP conclusions.(increased hepatocyte hypertrophy, hepatocyte necrosis & incr. in renal tubule adenomas. See Pathology Report Doc# 004855		Minimum 004370 005203 005590
83-3(a) Developmental Toxicity Study Species: rat Interntl. Res. and Develop. Co 401-054; 3/21/80	Glyphosate Tech. 98.7%	242516	Teratogenic NOEL > 3500 mg/kg/day (HDT). Maternal NOEL = 1000 mg/kg Maternal LEL = 3500 mg/kg/day (inactivity, death, stomach hemorrhages reduced body wt. gain. Fetotoxic NOEL = 1000 mg/kg/day. Fetotoxic LEL = 3500 mg/kg/day. Doses: 0, 300, 1000 & 3500 mg/kg/day A/D ratio = 1000/1000 = 1		Minimum 000119

TOXCHEM NO. 661A- N-(Phosphonomethyl)glycine FILE LAST PRINTED: 03/26/91

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COVERAGE/ DOCUMENTS
83-3(b) Developmental Toxicity Study Species: rabbit Interntl. Res. and Develop. Co 401-056; 2/29/80	Glyphosate Tech. 98.7%	242516	Teratogenic NOEL > 350 mg/kg/day (HDT). Fetotoxic NOEL > 350 mg/kg/day Maternal NOEL = 175 mg/kg/day. Maternal LEL = 350 mg/kg/day. (death, soft stools, nasal discharge. Levels tested: 0, 75, 175, 350 mg/kg/day A/D ratio = 125/350 < 0.5		Minimum 000120 000119
83-3(b) Developmental Toxicity Study Species: rabbit IBT 561-05275	Tralomethrin Tech.		IBT Invalid		Invalid 000270
83-3(b) Developmental Toxicity Study Species: rabbit IBT J-568, BTL 71-36; 6/30/72	Glyphosate TECH.	009856	IBT Invalid		Invalid 000266 003853
83-4 Reproduction-3 generation Species: rat IBT B-566; 7/26/73	Glyphosate TECH		This study is unacceptable. IBT invalid per Canadian reevaluation 4/8/81		Invalid 000276 Invalid 000280 Invalid 002195
83-4 Reproduction-3 generation Species: rat Bio/dynamics Inc. 77-20663; 3/31/81	Glyphosate Lot # XNJ-64	245909 247793	Systemic NOEL = 10 mg/kg/day. Syst. LEL = 30 mg/kg/day based on renal focal tubular dilation in male F3b weanling.		Supplementary 001862 Minimum 002124
Feeding-21 day Species: rabbit Interntl. Res. and Develop. Co 401-168; 3/10/82	Glyphosphate Tech.	247228	NOEL = 1000 mg/kg/day. LEL = 5000 mg/kg/day. (Slight erythema and edema). Levels tested: 0, 100, 1000 & 500 mg/kg/day		Minimum 001814
82-1(a) Feeding-3 month Species: rat IBT B1020, BTL 71-5; 6/26/72	Glyphosphate CP (N-phos-phoro-methyl glycine)		IBT Invalid		Invalid 002179 003853

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COVERAGE/ DOCUMENT#
82-1(a) Feeding-3 month Species: mice Bio/dynamics Inc. 77-211; 12/31/79	Glyphosphate Tech.	242799	NOEL = 10,000 ppm. LEL = 50,000 ppm (reduced body weight gain)		Supplementary 000254
82-1(a) Feeding-3 month Species: rat IBT BTL 7157, B 1020; 6/6/72	Glyphosphate CP 67573 Tech.		IBT invalid (evaluation date 9/14/72)		Invalid 002179
82-1(a) Feeding-3 month Species: rat Monsanto ML-86-351/EHL86128; 11/30/87	Glyphosate tech LotXLG161 95.2% purity white powdery solid	405594-01	Range Finding: In male rats, possibly increased serum phosphorus & potassium values at 1000, 5000, & 20,000 ppm; increased serum glucose val at 5000 and 20,000 ppm; increased serum BUN and alkaline phosphatase values at 20,000 ppm; pancreatic lesions in male rats at 20,000 ppm. In female rats, possibly increased serum phosphorus and potassium values at 1000, 5000, and 20,000 ppm. Levels tested in Sprague-Dawley rats ; 0, 1000, 5000, and 20,000 ppm.		Acceptable 006909
82-1(a) Feeding-3 month Species: rat Interntl. Res. and Develop. Co 401-050	Aminomethyl phosphonic acid (plant metabolite glyphosate)	241351	NOEL = 400 mg/kg/day LEL = 1200 mg/kg/day (weight loss, histopathologic lesions of the urinary bladder).		Minimum 000256
82-1(b) Feeding-3 month Species: dog IBT C-1021, BTL 71-58; 6/19/72	Glyphosphate Tech.	009856	IBT invalid		Invalid 000263 002177
82-2 Dermal-3 week Species: rabbit IBT 601-05044;BTL 7	Glyphosphate Tech		IBT-invalid		Invalid 000279
84-2(a) Mutagenic-Ames Species: Litton Bionetics Inc. 32547; 6/22/76	Glyphosphate Tech	242516	Negative up to 100 ug/plate (NDT)		Minimum 000271 000275

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COVERAGE/ DOCUMENT#
84-2(b) Mutagenic-DNA repair test Species: rat hepatocytes Monsanto AM-83-181; 10/83	Glyphosphate Tech.	251737	Negative for DNA damage at conc. between 1.35 x 10-5 and 1.25 x 10-1 ag/ml.		Acceptable 003868
84-2(b) Mutagenic-in vivo cytogenetic Species: bone marrow Monsanto ML-83-236; 10/20/83	Glyphosphate Tech.	251737	Negative at 1000 mg/kg		Unacceptable 003868 Acceptable 004348
84-4 Mutagenic-(HGPRT) Species: CHO cells Monsanto ML-83-155; 10/20/83	Glyphosphate Tech	251737	Not mutagenic with or without metabolic activation		Acceptable 003868
84-4 Mutagenic-range finding Species: ? Monsanto ML-83-60; 10/21/83	Glyphosphate		Range finding. Negative at dose level between 200 - 1000 mg/kg		Acceptable 003868
84-4 Mutagenic Species: mice IBT E-567; BTL71-35; 1/24/72	Glyphosphate Tech.	009856 234134	IBT Invalid		Invalid 003853 000271
84-4 Mutagenic-dominant lethal test Species: mice Interntl. Res. and Develop. Co 401-064; 4/16/80	Glyphosphate Tech. 98.7%	242516	Negative up to 2000 mg/kg. Levels tested: 0, 200, 800 and 2000 mg/kg		Minimum 000120
84-4 Mutagenic- host med. Species: rat IBT 623-07508	Glyphosphate		Negative up to 100 ug/plate (:DT). Invalid per Dynamac #68--01-6561, report 12/27/83		Invalid 000275 000270 000275

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-4 Mutagenic-microorganisms Species: microbes Inst. of Environ Tox. 7/20/78	Glyphosphate Tech. 98.4%		(1) Rec-assay (with B. subtilis) negative at 2000 ug/disk. (2) Reverse mutation with & without liver metabolic activation (with S. typh.) negative. (3). Salmonella mutagenicity negative at 1 1,000 ug/plate.		Minimum 000258
Risk assessment Species: EPA					002860
Percutaneous absorption Species: man Monsanto UM-81-346; 8/30/83	Glyphosphate (Roundup formulation)		Ninety seven percent of dose applied to skin was present in washes. Roundup was poorly adsorbed through human skin IN VITRO.		Acceptable 004362
Registration standard	Glyphosate		Tox. Chapter - 6/19/85 Revision - 3/1/88		007987
81-7 Neurotoxicity-acute delayed Species: hen IBT 8580-09117BTL-7682; 12/17/76	Glyphosphate Tech. CP6 7573 Lot# GN-68 94% a.i.	229184 00054494	Invalid due to missing raw data, use of animals with disease.		Invalid 004609
81-8 Neurotoxicity Species: hen IBT 8580-09117; 12/22/76	Glyphosphate Tech.		NOEL = 7.5 mg/kg (only level tested) IBT-invalid/scientific review		Invalid 000279 004465
82-6 Cholinesterase inhibition Species: rat IBT 601-06527,BTL 75-3; 3/7/73	Glyphosphate Tech.		IBT Invalid		Invalid 000279 000270
85-1 Pharmacokinetics Species: ? Monsanto 830109; 10/23/83	Glyphosphate Tech.	251737	t 1/2 of 7.6 hours (M) t 1/2 of 4.2 hours (F)		Acceptable 003868

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
85-1 Metabolism-elim of C14; IM inj Species: Rhesus monkey Monsanto MA-81-349; 4/1/83	Glyphosphate C14 Tech.		The C14-glyphosate was rapidly excreted in the urine following intramuscular injection.		Acceptable 004362
85-1 Metabolism Species: rat Monsanto Internat Res. and Dev 297 & 309; 6/15/73	Glyphosphate C14 95-98%		90-100% clearance of a single oral or i.p. dose in 120 hr. Females absorbed 3X as much as M. Levels tested: 0, 10, 100 ppm in die. for 14 days Only minimal residues of 0.1 ppm or less retained in tissues after 10 day withdrawal period. Supplementary because purity, activity of label used in repeated dose study not given; data for metabolites in excreta not provided.		Supplementary 004465
85-1 Metabolism Species: rat Monsanto MRL-7215;MRL7286; 3/21/88	Glyphosphate 14C purity > 99%	407671-01 407671-02	Thirty - 36% of orally administered glyphosate is absorbed. Glyphosate is excreted unchanged in the feces and urine (97.5% minimum). The only metabolite formed is AMPA, in the excreta, at less than 1% of the absorbed dose remains in the tissues and organs, primarily bone. Repeated dosing at 10 mg/kg does not significantly the metabolism,distribution,or excretion of glyphosate.		Guideline 006909
85-2 Metabolism - dermal absorption Species: monkey Monsanto MA-81-369; 4/1/83	Glyphosphate C14 Tech.		C14-glyphosate binds to skin and can not be removed by washing or systemic excretion. Only 50% of dose accounted for.		Unacceptable 004362
Metabolites			Casuell # 037C (Aminomethyl phosphonic acid). Casuell# 509E (Isopropylamino salt of glyphosate). Casuell# 788A (Sodium glyphosate). N-Nitrosoglyphosate, Casuell# 604AAB (Sodium salt of N-Nitroglyphosate)		
Peer Review Species: EPA, Toxicology Branch	N-(Phosphonomethyl) glycine				004324
Oncogenic Species: mouse	Glyphosate	00130406	The historical control data showed that the incidence of renal neoplasms in male CD-1 mice ranged from 0 to 3.3% at Bio/dynamics (the laboratory that performed the glyphosate mouse oncogenicity study), 0 to 4.7% at Hazleton, 0 to 1.7% at IRDC, 0 to 3.3% at Litton Bionetics, and 0 to 1.4% in Japan (Japanese Institute for Environmental Toxicology). The range of incidence of 0 to 7.1% reported by Monsanto in their November 10, 1988 meeting with the Agency was taken from the data on F1 male mice in reproduction studies at Hazleton. These F1 data could not be further substantiated by Monsanto and therefore, cannot be used to support the Monsanto position.		007252

TOXICHEM NO. 661A- N-(Phosphonomethyl)glycine FILE LAST PRINTED: 03/26/91

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Peer Review Species:	Glyphosate				007738
81-1 Acute oral LD50 Species: rat Younger Labs Inc. Y-70-90; 9/18/70	Glyphosphate Tech.	009856	LD50 (M & F)= 4320 (3930-4750) mg/kg	3	003853
81-1 Acute oral LD50 Species: rabbit IBT A-2277, BTL 72-189; 12/6/72	Glyphosphate Tech. 35% w/v in methylcellulose	112791	LD50 = 3800 (2836-5092) mg/kg. IBT valid	3	003853 000278 000264
81-1 Acute oral LD50 Species: rat Younger Labs Inc. Y-77-16; 2/18/77	60% WSP, 1.5% Na-glyphosate (plant metabolite of glyphosate)		LD50 > 10,000 mg/kg (highest level tested). Reduced appetite for one 1 day.	4	Minimum 000272
81-1 Acute oral LD50 Species: rat Internatl. Res. and Develop. Co 401-349; 6/19/85	2,4D-isopropylamine salt 11.1% Glyphosate 13.3%	262331	LD50 (F) = 3328 (1854-5942) mg/kg. LD50 (M) = 4081 (3126-5326) mg/kg.	3	Guideline 005990
81-1 Acute oral LD50 Species: rat Bio/dynamics Inc. 5887-85; 10/25/85	Glyphosate 16.5%; Dicamo..7.0%	401103-02	LD50 (M) = 4300 mg/kg. LD50 (F) = 3600 (2669-4531) mg/kg. LD50 (M&F) = 4000 (3606-4394) mg/kg.	3	Guideline 006045
81-2 Acute Dermal LD50 Species: rabbit Younger Labs Inc. Y-70-90; 9/18/70	Glyphosphate Tech.	009856	LD50 (F) => 7940 mg/kg LD50 (M) => 5010 mg/kg	3	003853

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-2 Acute Dermal LD50 Species: rabbit Younger Labs Inc. Y-77-16; 2/10/77	480 WSP, 1.5% Na-glyphosate		LD50 > 7,940 mg/kg (reduced appetite for three days)	3	Supplementary 000272
81-2 Acute Dermal LD50 Species: rabbit Internti. Res. and Develop. Co 401-350; 6/19/85	2,4D-isopropylamine salt 11.1% Glyphosate 13.3%.		LD50 > 5000 mg/kg	4	Guideline 005990
81-2 Acute Dermal LD50 Species: rabbit Bio/dynamics Inc. 5088-85; 10/25/85	Glyphosate 16.5%; Dicamo..7.8%	401103-05	LD50 > 5000 mg/kg.	4	Guideline 006045
81-3 Acute Inhalation LC50 Species: rat IBT 443-07290; 5/28/75	Glyphosphate Tech.		IBT Invalid		Invalid 000279
81-3 Acute Inhalation LC50 Species: rat IBT T-2279; 11/7/72	Glyphosphate 41% formulation MON 2139	009856	IBT Invalid		Invalid 000265 000278 003160
81-3 Acute Inhalation LC50 Species: rat Monsanto Environ. Health Lab 86125; 12/4/86	2,4-Dichlorophenoxy-acetic acid; isopropyl-amine..11.1%; Glyphosate 13.3%	400855-01	LD50 (M) = 3.1 (0.0-4.1) mg/L. LD50 (F) = 4.3 (2.8-5.7) mg/L. LD50 (M & F) = 3.8 (2.9 - 4.4) mg/L	3	Guideline 006100
81-3 Acute Inhalation LC50 Species: rat Monsanto Environ. Health Lab 86147; 3/19/87	Roundup L&G, Lot XLG-289 purity 18.9%; Isopropyl-amine salt of glyphosate	401893-01	LD50 > 5.7 mg/L for 4 hrs (M & F). Doses: 3.6, 3.8, 5.7 mg/L analytical conc. in Sprague Dawley rats.	4	Guideline 006111

TERCHEM NO. 661A- N-(Phosphonomethyl)glycine FILE LAST PRINTED: 03/26/91

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-3 Acute inhalation LC50 Species: rat	Tech.		Data requirement has been waived.		006541
81-3 Acute inhalation LC50 Species: rat Monsanto 88046; 6/10/88	Polado PGR ; lot #XLT-94; 75.53% glyphosate as the sodium sesqui salt Glyphosate	407507-01	LC50 > 1.45 mg/l (M&F) for 4 hrs; no deaths; 5M & 5F Sprague Dawley rats at 1.45 mg/l (gravimetric) MMAD > 10.0 um.	3	Supplementary 006867
81-3 Acute inhalation LC50 Species: rat Monsanto 88046; 6/10/88	Polado PGR; Lot# XLI-94; 75.5% glyphosate as the sodium salt	407507-01	LC50 > 1.45 mg/L (both sexes) for 4 hrs. No deaths; 5 M & 5 F Sprague-Dawley rats at 1.45 mg/L (gravimetric). MMAD > 10.0 uM.	3	Supplementary 006867
81-3 Acute inhalation LC50 Species: rat Monsanto Environ. Health Lab EHL-88067; 10/25/88	Glyphosate 16.5%; Dicamo..7.0%	401103-04	LC50 (M) = 0.82 (0.28-1.21) mg/L. LC50 (F) = 1.54 (1.16-2.19) mg/L. LC50 (M&F) = 1.14 (0.86-1.46) mg/L	3	Guideline 006045
81-4 Primary eye irritation Species: rabbit Younger Labs Inc. Y-70-90; 9/18.70	Glyphosphate Tech.	009856	P.I.S. = 12.6/110 at 1 hr.		Minimum 000265 000278
81-4 Primary eye irritation Species: rabbit Younger Labs Inc. Y-75-150; 6/30/75	Glyphosphate Tech.		Maximum score 26.6/110 at 24 hr. Severe erythema erythema, slight to moderate edema, copious discharge.		?
81-4 Primary eye irritation Species: rabbit Younger Labs Inc. Y-77-16; 2/18/73	60% USP, 1.5% Na-glyphosate		PIS = 0 at 48 hrs. Slight to moderate conjunctivitis.	3	Minimum 000272

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-4 Primary eye irritation Species: rabbit Internat. Res. and Develop. Co 401-351; 6/19/85	2,4D-isopropylamine salt 11.1% Glyphosate 13.3%	262331	Day 1: corneal opacity (3/6), redness, chemosis, discharge, petechiae, blanching, corneal peeling and corneal vascularization.	1	Guideline 005990
81-4 Primary eye irritation Species: rabbit Bio/dynamics Inc. 5889-85; 10/25/85	Glyphosate 16.5%; Dicamb..7.0%	401103-05	Day 21: corneal opacity, conjunctive irritation & ulceration.	1	Guideline 006045
81-5 Primary dermal irritation Species: rabbit Younger Labs Inc. Y-70-90; 9/18/70	Glyphosphate Tech.	009856	PIS = 0.0/8 (24 hr. exposure)	4	003853
81-5 Primary dermal irritation Species: rabbit Younger Labs Inc. Y-77-14; 2/18/73	40% WSP, 1.5% Na-glyphosate		PIS = 6.5 at 72 hours. Severe defatting effect persisted up to 72 hours. Skin sloughed off in 14 to 72 hours. No injury in depth.	2	Minimum 000272
81-5 Primary dermal irritation Species: rabbit Internat. Res. and Develop. Co 401-351; 6/19/85	2,4D-isopropylamine salt 11.1% Glyphosate 13.3%	262331	No irritation reported.	4	Guideline 005990
81-5 Primary dermal irritation Species: rabbit Bio/dynamics Inc. 5889-85; 10/25/85	Glyphosate 16.5%; Dicamb..7.0%	401103-06	72 hrs.: slight erythema (1/6). day 7: clear.	3	Guideline 006045
81-6 Dermal sensitization Species: guinea pig Bio/dynamics Inc. 4234-83; 10/7/83	Roundup	252142	Roundup was not a skin sensitizer		Minimum 004362

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-6 Dermal sensitization Species: guinea pig Bio/dynamics Inc. 80-85-000; 7/22/85	Glyphosate Tech.		Glyphosate was not a skin sensitizer.		Minimum 004362
81-6 Dermal sensitization Species: guinea pig Bio/dynamics Inc. 6046-86; 12/11/86	2,4-Dichlorophenoxy-acetic acid; Isopropyl-amine..11.1%; Glyphosate 13.3%	401069-01	Nonsensitizing.		Guideline 006100
81-6 Dermal sensitization Species: guinea pig Bio/dynamics Inc. 5911-85; 12/17/85	Glyphosate 16.5%; Dicamo..7.0%		Sensitizing agent.		Guideline 006045
Acute intraperitoneal LD50 Species: rat Younger Labs Inc. Y-75-112; 6/20/75	Glyphosphate Tech. (10% in corn oil)		LD50 = 470 (410-540) mg/kg		000279
Acute subcutaneous LD50 Species: rat Younger Labs Inc. Y-75-151; 6/23/75	Glyphosphate Tech. 10 & 20% in corn oil		LD50 > 5010 mg/kg (NOT). Reduced appetite and activity. (No deaths)		000279
Acute subcutaneous LD50 Species: rat Younger Labs Inc. Y-75-151; 6/3/75	Glyphosate Tech 10 & 20% in corn oil		LD50 > 5,010 mg/kg (NOT). Reduced appetite & activity (No deaths).		000279

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR 4 1985

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Consensus Review of Glyphosate
Caswell No. 661A

TO: Robert Taylor
Product Manager
Herbicide - Fungicide Branch
Registration Division

On February 11, 1985, a group of Toxicology Branch personnel met to evaluate and discuss the data base on Glyphosate, and in particular the potential oncogenic response of Glyphosate.

A. The following persons were in attendance:

Theodore M. Farber, Ph.D.
Chief, Toxicology Branch

Louis Kasza, D.V.M., Ph.D.
Pathologist

Bertram Litt, Statistician

Herbert Lacayo, Ph.D.
Statistician

Reto Engler, Ph.D.

William Dykstra, Ph.D.
Reviewer

Steve Saunders, Ph.D.

Laurence Chitlik, D.A.B.T.

The signatures above indicate concurrence with this concensus report.

B. The material available for review consisted of a package issued on January 25, 1985 (attached) and a letter from Monsanto (dated February 5, 1985), rebutting the significance of renal mouse tumors.

C. Evaluation of the Facts:

1. Long-term/Pivotal Studies:

a) A 26-month rat study showed a NOEL at 30 mg/kg/day which was the HDT. The oncogenic potential at this level was negative, corroborated by an outside consultant. Although some thyroid tumors were observed in female rats in this study they were generally discounted in their significance, in and of themselves. However, it should be noted that on a mg/kg/day basis the exposure of rats was less than 1/100 of the exposure of mice (4,500 mg/kg/day). Since a toxic, or MTD, level was not reached in this study, the panel raised the conjectural issue that at toxic levels at or close to a MTD, tumors might have been induced.

b) The NOEL in a rat 2 generation reproduction study was 10 mg/kg/day. In separate teratogenicity studies feto toxic effects were noted in rats and rabbits at levels which caused significant maternal toxicity, including death; terata were not observed (ibid). These results were, however, not entered into the discussion on Glyphosate.

2. Mutagenicity Assays:

Glyphosate was tested for mutagenic activity (1) Reverse Mutation in S. typhimurium. and E. coli with and without microsomal activation, (2) Ames Assay with and without activation, (3) CHO cells with and without activation, (4) DNA repair in rat hepatocytes, (5) Rec-assay in B subtilis, and (6) Dominant lethal assay in mice. All these tests were negative, tests 1-3 are fairly well predictive of oncogenic response while 4-6 are less appropriate. An in vivo bone marrow cytogenetics study was also performed. It was negative, but scientifically not acceptable. In summary, several appropriate and scientifically acceptable tests are supportive of non-oncogenic potential of Glyphosate.

3. In the chronic mouse study carried out by Biodynamics (#BDN 77-420) renal tubule adenomas were observed in males.

Dose (ppm)	0	1000	5000	30,000
No. Exposed	49	49	50	50
Tumors	0	0	1	3

See review of W. Dykstra (dated 9/4/84).

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This is a rare tumor even in Charles River CD-1 male mice. Biodynamics historical data (included in package) show that this tumor was observed only 3 times in 14 male control groups ranging in size between 51 and 60 mice.

The probability of observing this tumor 4 times or more in 198 mice (the total number of mice examined in the Glyphosate study) is p = 0.0064 when considering the historical control of the same laboratory. Even considering other reported historical controls, the p-value is low, about 0.01 indicating that it is very unlikely that the glyphosate test group is consistent with any historical controls. (See review by Dr. Lacayo).

In addition, the response rate (see above) seems to be related to the dose.

Therefore, it was the concensus of the group that the renal tubular adenomas were related to compound administration, since their frequency was <u>not</u> consistent with the historical controls and there is a trend indicating dose dependency.

3a. The group noted that there were other non-oncogenic, i.e., toxicological changes apparant in the kidney and liver e.g., central lobular hepatocyte hypertrophy and necrosis and chronic interstitial nephritis in males and proximal tubule epithelial basophylia and hypertrophy in females. The group discussed the possibility of kidney irritation and formulation of crystals but noted that kidney or bladder precipitaters were not reported for this assay. Therefore, a conclusion mitigating the renal tumors could not be reached. (See page 10 of contractor review).

D. <u>Other Considerations</u>:

The review panel recognizes that the exposure of mice was at a very high level 4.5 g/kg/day. Precipitation of Glyphosate in the kidneys might have occurred but none was reported. The panel believes that additional sectioning of new blocks of male kidneys might help in the interpretation of the study results. The kidney tumors as reported, were unilateral (pers. communication by Dr. Dykstra, after the panel meeting); additional histopathology could resolve the issue of whether this is a valid observation or due to not "finding" the tumors in the particular block analyzed.

The panel also believes that realistic exposure assessment, both for dietary and worker exposure are of singular importance. For example, the limit of detecting residue tolerances may overestimate exposure. Particular emphasis also should be given to residues in water, since Glyphosate has been used for aquatic weed control (EUP) and this use may become the subject of a permanent registration.

E. <u>Classification of Glyphosate</u>:

In accordance with EPA proposed guidelines (FR of Nov. 23, 1984) the panel has classified Glyphosate as a Category C oncogen.

ADDENDUM:

The letter by Monsanto (Feb. 4, 1985) has been considered in these deliberations. Several of the issues raised are, in fact, addressed in the above deliberations, although not point by point. A point by point rebuttal, including those points with little merit, will be done in addition to this evaluation.

Attachments

cc: B. Coberly
Caswell No. 661A

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008527

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 26 1985

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Use of historical data in determining the weight of evidence from kidney tumor incidence in the Glyphosate two-year feeding study; and some remarks on false positives

TO: Reto Engler, Chief
Scientific Mission Support Staff
TOX/HED/OPP (TS-769C)

FROM: Herbert Lacayo, Statistician
Scientific Mission Support Staff
TOX/HED/OPP (TS-769C)

Herbert Lacayo 2/26/85

THRU: Bertram Litt, Statistics Team Leader
Scientific Mission Support Staff
TOX/HED/OPP (TS-769C)

BACKGROUND

The Glyphosate feeding study (EPA Reg. #: 524-308, Caswell #: 661A, Accession #: 251007-014) on Charles River CD-1 mice generated renal tubular adenomas in male mice at the 5000 and 30000 ppm dose levels. The registrant (Monsanto) claims that such tumors are "unrelated to treatment." (ref.1). In support of that they provide historical data from Bio/dynamics and two other laboratories (ref.2).

With respect to historical data we note the large number and variety of factors which influence the life history of rodents in chronic studies. Hence, it is generally agreed that the most relevant historical controls are experiments from the subject laboratory studied within a 3 to 4 year "window" (ref.3).

SUMMARY

The main purpose of this memo is to show one way historical data may be used to evaluate the significance of tumors in the glyphosate feeding study. When these data are so used we can conclude that Glyphosate dosing has a statistically significant effect (at the p = .006 level) in the production of kidney tumors in male mice. The appropriate procedure is outlined in the next section entitled Use of Historical Data. The last Section, Remarks on False Positives, addresses some comments by Monsanto (Ref.1) on this subject. That section outlines some of the weaknesses in Monsanto's position.

USE OF HISTORICAL DATA

The following information was derived from Reference 2.

Data Source*	p (est.of tumor rate)	Sigma (est.of standard deviation)
Bio/dynamics	.00368	.00212
IRD Corp.	.00437	.00109
Combined	.00399	.00094

The value p = .00368, derived from Bio/dynamics data is a reasonabl choice to use as a historical control. The data are from the same laboratory that performed the Glyphosate study and are within the appropriate 3-4 year time "window" (ref.3). Further, the standard deviation of the estimate is reasonably small.

We will now examine the Monsanto contention that the kidney tumors are unrelated to treatment. (i.e. Glyphosate has no effect on kidney tumors). First, consider the tumor rate in the Glyphosate Study: 4/198 = .0202 ---

In contrast, Bio/dynamics has the lower historical rate:

3/815 = .00368

The relevant question is: What is the probability that the 198 CD-1 mice in the Glyphosate study will produce by pure chance 4 or more mice with kidney tumors? Another way of stating this is - How likely are we to have a tumor rate of .0202 --- for the Glyphosate study given that the historical rata is .00368?

Questions of this type may be answered from manipulation of the relevant distribution which, in this case is the Binomial:

$$P(r \text{ out of } n \text{ mice have tumors}) = \binom{n}{r} p^r q^{n-r}$$

Where: n = the # of male mice in the study

r = the # of male mice with kidney tumors

p = .00368, the historical probability that an individual male mouse will develop kidney tumors.

q = 1 - p

*This does not include Hazleton Laboratories America, Inc. due to the small sample size of that data set

Using the above distribution and elementary but tedious calculations, we generate the following table:

# of mice with tumor	Probability that r or more mice will have tumors in a study with 198 male mice
r = 0	1.
1	.516177
2	.165711
3	.037443
4	.006481

This last table indicates that based on a historical rate of p= .00368 that the probability of seeing 3 or more mice with kidney tumors is about .037; and the probability of seeing 4 or more such mice (i.e. seeing what in fact happened) is about .0064. We note that even considering data from I.R.D., the p value is about .01.

Under such circumstances a prudent person would reject the Monsanto assumption that Glyphosate dosing has no effect on kidney tumor production. Another way of saying this is that if Glyphosate were truly unrelated to kidney production we would expect to see 4 or more tumors in less than 1 out of 100 experiments of the type sponsored by Monsanto. Thus, Glyphosate is suspect.

REMARKS ON FALSE POSITIVES

In ref. 1 Monsanto notes that "...if 20 types of lesions were evaluated at a probability level of .05, the number expected to be positive would not be one in 20, but rather the probability would be 64 in 100, an unacceptably high value..." Monsanto is referring to the well-known fact that by examining enough data it is likely that one will find an excess of some tumor type by chance alone; thus generating a false positive.

The Monsanto argument required the following assumptions:

1. A mouse may develop 20 distinct and independent (in the statistical sense) types of tumors.
2. The probability of each tumor type in a typical mouse is .05.

It follows from the above that:

$$P(\text{a mouse has at least one tumor}) = 1 - .95^{20} = .6415$$

Hence in 100 mice one would on the average see 64 with tumors. Monsanto proposes to avoid this "problem" of false positives by analyzing the study" ...at the .01 probability level."

We disagree with the Registrants position. First, even if one did analyze the study at the .01 level as they suggest it would still result (using the same mathematics as before) in seeing 18 mice out of 100 with tumors. And hence one still has the problem of false positives from the registrant's viewpoint. But this causes something worse from a regulatory viewpoint. We have decreased the false positive rate (i.e., the probability of saying that a chemical causes tumors when in fact it does not) at the cost of increasing the false negative rate (i.e., the probability of saying that a chemical doesn't cause tumors when in fact it does). The Registrant wishes to avoid false positives while those concerned with the public health wish to avoid false negatives. Hence, for this reason alone Monsanto's argument is unacceptable.

We further disagree as follows:

1. The two assumptions needed to support the Monsanto argument are themselves in need of support (especially the requirement for statistical independence).
2. False positive results are less likely to occur with rare tumors (ref. 5). And the tumors in question are rare.

Viewpoint is a key issue. Our viewpoint is one of protecting the public health when we see suspicious data. it is not our job to protect registrants from false positives. We sympathyze with the Registrants problem; but they will have to demonstrate that this positive result is false.

Finally, we mention that none of the tumors occurred in the control or low dose groups. Instead there was one at 5000 ppm and 3 at the 30000 ppm dose level. This together with the previous comments make it likely that there is a dose-tumor relationship for Glyphosate.

REFERENCES

1. Letter from Monsanto (signed by Frank. S. Serdy) to EPA (Attn: Robert J. Taylor) dated Feb. 5, 1985.

2. Letter from Monsanto (signed by Robert W. Street) to EPA (Attn: Robert J. Taylor) dated March 20, 1984.

3. J.K. Haseman, et al: Use of Historical Control Data in Carcinogenicity Studies in Rodents - Toxicologic Pathology - 12:126-134. 1984.

4. TOX Branch Memo from William Dykstra to Robert Taylor dated 9/4/84.

5. T.R. Fears et al: False-Positive and False-Negative Rates for Carcinogenicity. Cancer Research. 271:1941-1945. July 1977.

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008521

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

December 4, 1985

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: William Dykstra, Ph.D.
Reviewer, Toxicology Branch, TS-769

FROM: Louis Kasza, D.V.M., Ph.D.
Pathologist, Toxicology Branch, TS-769

SUBJECT: Glyphosphate -- Evaluation of Kidney Tumors in Male Mice.
Chronic Feeding Study.

INTRODUCTION:

Tumors (0 (1)*; 0; 1; 3) were found in the kidneys of male mice at [illegible]. There were differences in the pathology [illegible] as to whether the small localized change in one kidney of the control group (#1028) represented a tumor or not. In order to provide more information, the Agency recommended the preparation of three (3) additional sections from each kidney in the male groups. "The lesion was not present in the recut specimens from that animal" in the control group (#1028). In the final re-evaluation of the questionable control kidney slides (#1028), the conclusion was formulated that "The pathology staff at Bio/dynamics and I (Dr. McConnell) reviewed the lesion and concur that it may be representative of a developing tumor".

MATERIALS AND METHODS:

I (Dr. Kasza, Branch Pathologist) requested all kidney sections from male mice. After selection of slides from all animals in which kidney tumors were diagnosed, I studied them under the microscope.

RESULTS:

There was no difference in diagnoses between my and other pathologists' diagnoses with respect to kidney tumors in mid- (#3023) and high dose (#4029, 4023, 4041) groups. With regard to the questionable male control kidney (#1028), it is my opinion that the presence of a tumor can not definitely be established. My interpretation is similar to the conclusion of Bio/dynamics' pathology staff and Dr. McConnell, that the lesion "may be" a proliferative change having the potential to lead to the development of a frank tumor. But as the tissue can be seen under the microscope as a small well-demarcated focal cell aggregate morphologically different from the healthy looking surrounding kidney tissue, this morphological alteration does not represent a pathophysiologically significant change.

*In parentheses is the review pathologist's findings.

cc: T. Farber
W. Burnam
R. Engler
R. Zendzian

END